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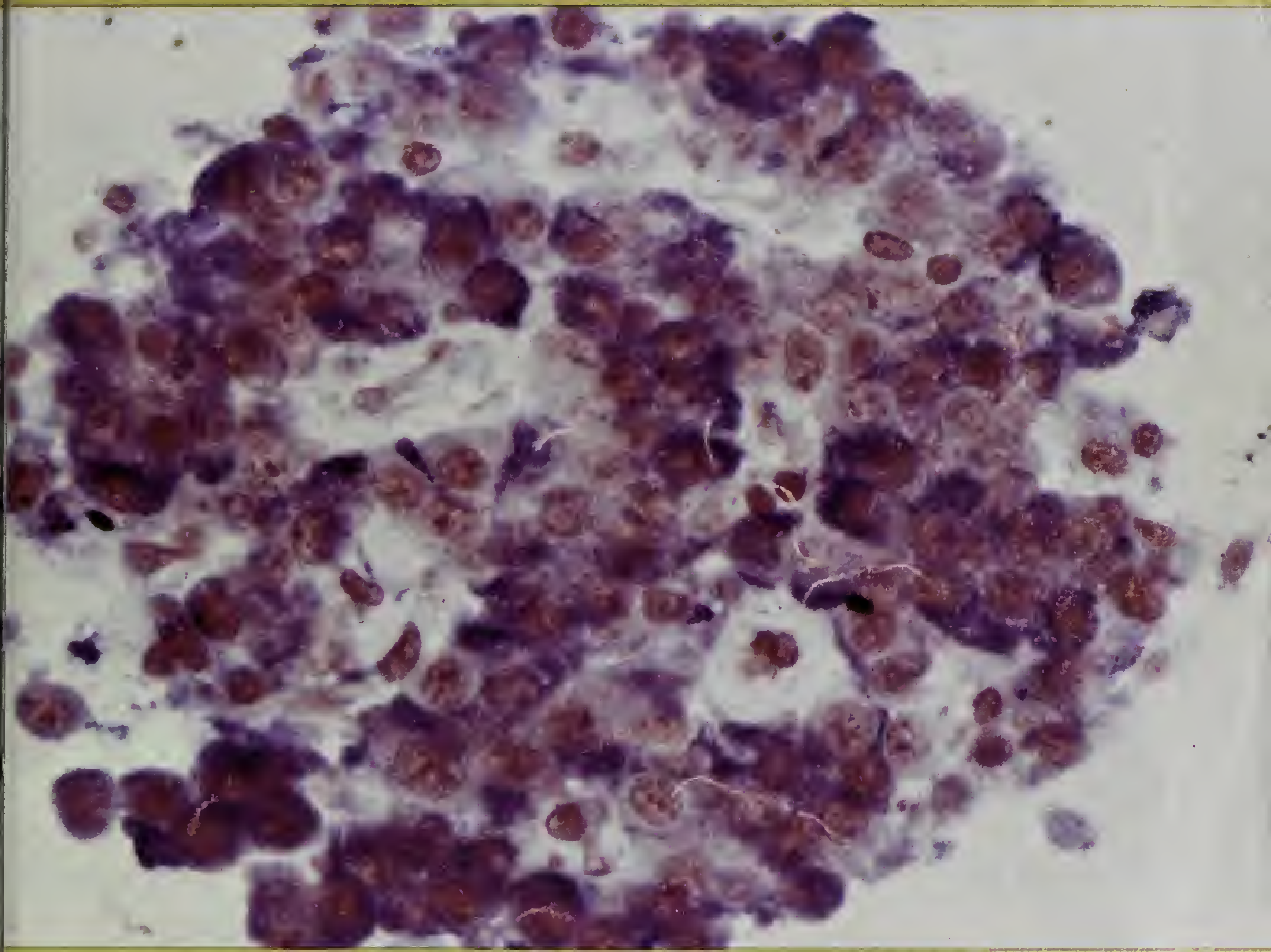

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David Sutherland, M.D.

JANUARY 1979

"Diabetes Mellitus"
Special Issue

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Contents — January, 1979

COVER PHOTOGRAPH — Human Islet of Langerhans
David Sutherland, M.D. 50

PRESIDENT'S LETTER — Litigation Alligators
Robert S. Flom, M.D.
President, Minnesota Medical Association 5

EDITOR'S NOTEBOOK — Minnesota Medicine: The Long and Short of It
Richard L. Reece, M.D.
Editor-in-Chief 7

EDITORIALS
Diabetes Mellitus — Past Present and Future
Leonard Mastbaum, M.D.
Guest Editor 9

Team Management of the Diabetic Patient
Judy M. Beriou, R.N., B.A. and
Carelyn P. Fylling, R.N., M.S. 11

ORIGINAL CONTRIBUTIONS
Genetic Aspects of Diabetes Mellitus
Richard A. King, M.D. and Jose J. Barbosa, M.D. 14

Obesity and Diabetes Mellitus
Frank Q. Nuttall, M.D. 19

Ocular Changes in Diabetes
Howard D. Gilbert, M.D. 22

Insulin Therapy — Things That Make a Difference
G.E. Cotton, M.D. and A.J. Sill, M.D. 31

Nutritional Management in Diabetes
Marion Franz, R.D., M.S. 41

Potential Future Modes of Therapy in Diabetes Mellitus
John E. Gerich, M.D. 46

SPECIAL ARTICLE — Living with Diabetic Children — A Family Affair
George M. Johnson, M.D. and Janice B. Johnson, B.A., M.S. 51

AMERICAN DIABETES ASSOCIATION
David L. Zuelke, President 55
List of Chapters, Branches and Units 65

MINNESOTA MEDICAL ASSOCIATION —
Syllabus for 1978 Annual Meeting
J.S. Welch, M.D. 59

MINNESOTA MEDICAL ASSOCIATION — Annual Meeting
S.V. Thorson, M.D. Chairman,
MMA Subcommittee on Scientific Assembly 21, 45, 64, 70

CLASSIFIED ADVERTISING 67

INDEX TO ADVERTISERS 56

Volume 62:1
Pages 1-70

MINNESOTA MEDICINE REPRESENTS

- Association of Neurologists of Minnesota
- Duluth Surgical Society
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President's Letter

Litigation Alligators

At the recent AMA Convention in Chicago a most difficult problem was widely discussed. A lawsuit in Pennsylvania against a number of medical organizations had been settled by some, including the AMA, in a fashion which seemed to others to be an abdication of previous stands as related to medical ethics. The American College of Radiology assessed its members a significant amount of money to fight this case which appeared to them to be worthy of defense on the grounds that settling would have forced practitioners, such as radiologists, to participate in the diagnostic and implied therapeutics of limited licensed practitioners.

Another suit was then filed by an AMA delegate and an alternate delegate against the AMA charging that the AMA Board of Trustees in settling the case had in effect changed the AMA code of ethics which it had no right to do without an action by the AMA House of Delegates.

Meanwhile, yet another suit has been filed in Chicago against the AMA and several specialty groups which would again seek remedies and punitive damages for an alleged restraint of trade upon limited practitioners who would seek fuller recognition and privileges by forcing themselves into the mainstream of medicine, not by demonstrating scientific excellence or knowledge, but by judicial fiat.

Impacting on all of these actions are the licensing laws of the various states, the Federal Trade Commission posture which has been allowed into the professional field by judicial decision on the assumption that competition for health care dollars is a more basic value than is guaranteed minimum performance by licensing laws and professional standards, and the ever increasing wresting of power by federal bureaus and commissions from the democratic elective process.

The House of Delegates committed itself to the fact that the Board of Trustees did act within its authority, that each physician has the right to choose (or reject) whom he/she will serve and that this right will be vigorously defended by all of medicine through the AMA.

While the wisdom and ramifications of these various actions remain yet to be seen and evaluated, several lessons and observations come to mind:

1. Second opinions, and as many as eight opinions, in the legal field fail to approach unanimity.
2. Unanimity of decision is essential to the assumption of a viable posture, and that unanimity is essential to maintaining the integrity of our professional principles. This is best achieved by integration of subgroup opinions into the most democratic process of arrival at consensus, which in my view, is through the Interspecialty Council in the case of MMA and through the House of Delegate representation in the case of AMA.
3. Government agencies removed from the democratic elected process can take actions which are not necessarily in the best interest of, for, or by the people of this country.
4. Physicians understand and are sympathetic to the points of view of other physicians, but can become emotional antagonists of one another in their attempts to decide upon courses of action.
5. Litigation cost vast amounts of money, must surely be a significant portion of the Gross National Product, and second opinion in this field is not a cost saving device. The adversary system has an inherent 50% mortality, and avoidance by settlement has a high morbidity, and attendant emotional strains and suffering are not as yet compensable.
6. Happy New Year and watch out for all those alligators.

Robert S. Flom

Robert S. Flom, M.D.
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Editor's Notebook

MINNESOTA MEDICINE: The Long and Short of It

When you read these words, 1979 will be here. What is special about 1979, you ask. Well, 1979 is MINNESOTA MEDICINE'S 60th birthday. Occasion enough, it seems to me, to lean back, gaze at the ceiling, and ponder our long and short term prospects.

Our long term prospects are excellent. After all, we have been around for 60 years, and we have a solid reputation among state and regional journals. Indeed 16 years ago, under Carl Rice's editorship, MINNESOTA MEDICINE was voted the outstanding State Medical Journal in the United States. Minnesota has always been a hotbed of medical and scientific talent, and, at least in my 13 years of editorial association with the Journal, has not been short on good manuscripts.

We now have the opposite problem — too many worthy manuscripts with too little space to publish them. Why so little space? Inflation — pure and simple. Last week, the American public received news that two dollars would now buy what one dollar would in 1967. With MINNESOTA MEDICINE, inflation is even worse — it costs us three times as much to publish one page as it did in 1967. Which is why our space has shrunk. Ten years ago, MINNESOTA MEDICINE averaged 154 pages an issue; our average in 1978 was 61 pages — precious little space for our prolific contributors.

Anyway, because of high inflation, a tight budget and limited space, we were unable to publish all accepted manuscripts in 1978. If you are the author of one of these accepted manuscripts, I have good news. In the next six months, we shall publish our backlog of manuscripts. Be patient: we have not forgotten you.

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Editorials

Diabetes Mellitus

Past, Present and Future

SCIENTIFIC FUTURISTS base their predictions on the past and the present. Civilization, they say, is on the "hinge of history," implying that the increasingly rapid pace of change observed today will produce a different world in the near future. The quality of our lives will change, presumably for the better.

Certainly these observations apply to diabetes. In both basic and clinical research, the rate of acquisition of new information has quickened, and the lag time between laboratory discovery and clinical implementation has shortened. Superficially it seems reasonable for us to expect a straight forward "cure" for diabetes. However, let us examine this thesis in historical perspective.

The Past

The story of diabetes is a chronicle plodding progress punctuated by major breakthroughs. The symptoms of diabetes were described in the Ebers Papyrus of 1550 B.C. The early Greeks observed the passage of copious urine and called the disease "diabetes", i.e. "a passing through." The Romans noted the sweetness of the diabetic's urine and added the term "mellitus," i.e. "sweet as honey."[1] In 600 B.C., Susruta taught that "honey urine" was incurable, and the Roman physician Aretaeus (81?-138 A.D.) agreed.[2] In general terms, he described the two varieties of the disease, one with "torpor, indolence and corpulence" (maturity-onset type), and the other with "a melting down of the flesh into sweet urine" (juvenile type). Noting that death occurred early in the latter type, he also alluded to a hereditary factor when he stated, "It is passed with the seed."[3]

Hundreds of years were to pass before there was any significant addition to our understanding of diabetes. Developments in the fields of chemistry and surgery were necessary prerequisites. In the 17th century, Willis redescribed the sweet taste of the diabetic's urine and established this as the first diagnostic sign.[4] Matthew Dobson (1735?-1784) chemically extracted a sweet substance from diabetic urine *and blood*. The French chemist Chevreul (1786-1889) demonstrated that the sweet substance was identical to grape sugar. The work of Claude Bernard (1813-1878), particularly his studies of the role of the liver in glucose metabolism, had far reaching effects on subsequent studies of diabetes. His pupil, Lancereaux (1829-1910) pointed out the relationship between diabetes and pancreatic lesions. Bouchardat (1806-1886), who initiated the modern treatment of diabetes, advocated carbohydrate restriction, periods of fasting and use of exercise to control glycosuria. He also introduced the concept of the diabetic patient's personal responsibility for his own care.[2]

In 1921, the world was astounded when Banting and Best, working in a borrowed laboratory without benefit of a budget, were able to prepare active extracts of pancreas which controlled the glucose levels in diabetic dogs. With the help of Collip and Macleod, Banting and Best were able to prepare sufficiently pure extract to begin human trials within two years.[5] As a result of their work, the lives of millions of diabetics have been extended. Insulin was hailed as a cure for diabetes; however, this advance, by allowing insulin-dependent diabetics to survive bouts of ketoacidosis, unmasked the long-term complications of diabetes mellitus — the retinopathy, nephropathy, neuropathies and accelerated atherosclerosis — with which we stuggle today.[6]

The isolation and purification of insulin is recognized as the major breakthrough to date in diabetes therapy, but the work of Banting and Best was built on that of earlier investigators. In 1869, Langerhans described the small nests of cells within the pancreas which now bear his name.[1] Minkowski in 1889 reported that complete extirpation of the pancreas produced diabetes in animals, thus allowing the creation of experimentally diabetic animals for further study. Laguesse (1893) suggested that the islets of Langerhans produced an internal secretion affecting carbohydrate metabolism, and in 1901, Opie showed that human diabetes was associated with destruction of, or injury to, the islets.[2] Moses Barron's observations on the degeneration of acinar tissue with preservation of islet cells in patients with pancreatic duct obstruction directly triggered Banting's plan for the isolation of insulin.[7] At least nine other groups of investigators had tried unsuccessfully to prepare useful pancreatic extracts before Banting and Best.[8]

Reprint requests to: Dr. Leonard I. Mastbaum, Clinical Studies Department, Mount Sinai Hospital, 2215 Park Avenue, Minneapolis, Minnesota 55404.

Since the launching of insulin, the pace of diabetes research has accelerated. Knowledge of the physiology of carbohydrate metabolism in general, and of the pathophysiology of diabetes mellitus in particular has burgeoned. The roles of other relevant hormones have been elucidated. All conceivable aspects of diabetes — definition, diagnosis, pathogenesis, management of acute and chronic complications, and social, political and psychiatric ramifications of the disease — have been scrutinized. There has been no breakthrough of the proportion of Banting and Best, but we have seen a steady flow of new information and improvements in therapy. The most significant recent research concerns the relationship of metabolic control of diabetes and the prevention of its long-term complications.

The Present

Diabetes affects five percent of the United States' population, and its prevalence is increasing by six percent per year. Insulin provides a preventative and an effective treatment for ketoacidosis, resulting in a dramatic decrease in death rates from this complication. Surgery is safer for the diabetic. Pregnancy no longer poses great danger to the diabetic mother and is more likely to result in a live birth. However, the observed incidence of blindness in diabetics is 25 times higher than that of the general population; renal disease occurs 17 times more frequently; there is a five-fold increase in the incidence of gangrene and a two-fold increase in heart disease; and the life expectancy of diabetics in the United States is one-third less than that of non-diabetics.[9]

We know much about the natural course of diabetes, but little of the underlying mechanisms. In this issue, Nuttall explores the relationship of obesity and diabetes.[10] King and Barbosa update our knowledge of the genetics of diabetes, bringing us the evidence for different genetic mechanisms in the insulin dependent and non-insulin dependent types.[11] Gilbert describes in detail what is seen in the course of diabetic retinopathy and discusses therapy.[12] Gerich summarizes the compelling evidence that vascular complications are a consequence of the metabolic abnormality.[13] Recent evidence suggests that viral infection may trigger the destruction of beta cells in some patients, and autoimmunity may play a role in others,[14] but in fact the exact cause or causes of diabetes are basically not defined. Furthermore, it is not clear whether hyperglycemia per se, insulin deficiency, or both is/are the culprit(s) in the production of the long-term complications. How well correction of hyperglycemia correlates with correction of insulin deficiency is also unknown.

There are significant recent advances in diabetes care. Timely photocoagulation of the retina saves vision.[12] Renal transplantation is feasible in the diabetic with end-stage renal diseases.[15] Newer vascular surgical techniques prevent loss of limbs in some diabetics with large vessel disease. A growing body of knowledge suggests that the long-term complications of diabetes are related to lack of sufficient control of the blood sugar, and an external artifical pancreas can provide such control temporarily.[13] Some of the articles in the issue indicate methods of improving control.* However, maintenance of optimum control is difficult, requiring very diligent attention to diet, insulin administration and other details of care. Even with great effort this goal is probably impossible to achieve by currently available methods in many patients.

The Future

The nature of medical research has been described as "a continuum flowing between the laboratory and the patient."[16] It is a continuum from the past to the future as well. Today's discovery in the laboratory will affect the care of patients with diabetes in the future. Clinical results will affect the course of laboratory research. The near future should be reasonably predictable, and the medium-range future at least discernible in outline.

I expect that a single etiology for what we now call "diabetes" will remain elusive. An isolated chemical abnormality, inappropriate hyperglycemia, has been the sine-qua-non of diagnosis of this syndrome with protean manifestations. In some patients different facets of the syndrome, e.g. hyperlipidemia or accelerated vascular disease, seem to predominate, and the degree of blood sugar elevation is minimal. Others with documented long-standing, poorly controlled hyperglycemia prove amazingly resilient to the expected long-term complications.

Perhaps our diagnostic acumen will sharpen as the clinical meaning of the differences between insulin deficiency and insulin resistance become clear. We may find as recently suggested by Turkington and Weindling,[17] that true diabetes with its attendant long-term complications results from insulin lack rather than from hyperglycemia. The author views true diabetes mellitus as the end result of destruction of the pancreatic islet cells with resultant deficiency of insulin. Such destruction may be related to any one or more of a number of insults, just as hepatic cirrhosis is the final pathway of many insults to the liver.

Our diabetes agenda is a full one. Acceptance of the gathering evidence that the chronic complications of diabetes are secondary to imperfect metabolic control necessitates renewed emphasis on helping our patients to achieve better control. By improved usage of our legacy of knowledge in nutrition, use of insulin, and patient education techniques as well as organization of our trained professionals,* we can accomplish much. While encouraging our diabetic patients to make full use of these tools, we must continue to seek a means of correcting the major endocrine abnormality of diabetes completely — by beta cell or pancreas transplantation, or by creation of a functional artificial beta cell. We must continue to unravel the possible causative factors in the hope that a more thorough understanding will enable us to prevent diabetes.

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*See article by Cotton and Sill on page 31 and by Franz on page 41.

Leonard Mastbaum, M.D.†
Guest-Editor

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*See TEAM Management of the Diabetic Patient, p. 11.

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Team Management of the Diabetic Patient

DIET, MEDICATION AND exercise are the basic components of daily diabetes care. Involved in the delivery of this care are many decisions and considerations regarding blood glucose determinations, other diagnostic procedures, physical examination plus a myriad of details from urine testing, injection and foot care techniques to dietary management and adjustments for illness and special occasions, as well as use of community resources. *All* of these factors need to be coordinated in the comprehensive care of the diabetic patient.

To achieve this coordination, the talents, skills, and expertise of several health disciplines must be unified into a team effort. The physician, nurse and dietitian compose the core of the team with the pharmacist, social worker, physical or occupational therapist or vocational counselor contributing when appropriate. Clearly the most important team member is the patient himself.

Barring an episode of major illness, the patient has direct contact with the physician and other health professionals for no more than six to 12 hours per year.[1] Accordingly, the patient is responsible for his own management 24 hours a day, making him the most "involved" member of the team. To function effectively in this role, he must be equipped with knowledge which enables him to make appropriate decisions between office or clinic visits. Therefore, optimal health care for the diabetic involves the coordinated input of the entire team to provide a health care program for education of the patient and management of his disease.

In functioning as a team, the various health professionals interview, assess the status of the diabetic patient from a number of viewpoints including his physical, emotional and educational needs, his ability to comply, his personal goals and management plan consistent with the individual's life style. At the time of initial diagnosis or of comprehensive re-evaluation, the physician obtains the patient's health history, completes a physical examination including a careful search for complications of diabetes, and orders appropriate laboratory tests. The nurse assesses the patient and his family members' attitudes and skills as well as their knowledge of, or ability to learn about, diabetes. In formulating a dietary prescription, the dietitian evaluates not only the individual's ideal body weight, but also his usual daily activity level and nutritional requirements. Based on this total assessment of the patient's physical, educational, emotional, and other needs, the physician can then best determine the general method of management for the patient's diabetes. Communicating all this information among team members, including the patient, enables them to develop a comprehensive, rational education and treatment program.[2]

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In soliciting the cooperation of the patient, the physician not only must impress upon the patient the needs for education and treatment, but he must also stress the importance of the patient's role in the management plan. To implement the education program requires instruction by each core health team member in his respective area as well as the input of the other health disciplines when needed. The services of these health professionals are available through the local hospital, clinic, community or regional agencies. Where they are unavailable, local health professionals should strive to implement these services to improve the care of patients in the area.

The professional health team members must continue to evaluate the patient's physical progress, his level of knowledge, his acceptance and compliance, and his success in applying the concepts learned. To augment the ongoing treatment and education plan, community resources such as diabetes education programs, public health nurses, community mental health units and local diabetes associations are available to the physician for patient referral as well.

For optimal care of the diabetic patient, the health care team including the patient must be dynamically involved in all phases of diabetes management including diagnosis, assessment, planning, treatment, education and evaluation. "Quality health care can only be achieved by informed patients cooperating with interested and knowledgeable health professionals."[3] Each health discipline's input is a vital link in assuring comprehensive health care for the diabetic patient.

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Genetic Aspects of Diabetes Mellitus

RICHARD A. KING, M.D., PH.D.* and JOSE J. BARBOSA, M.D.*

Diabetes mellitus is a genetically heterogeneous group of disorders and not a single genetic disease. Family and twin studies suggest that the genetic factors involved in adult-onset diabetes (AOD) and juvenile insulin-dependent diabetes (JIDD) are different. Immunogenetic studies in JIDD show a significant association between this type of diabetes and the major histocompatibility complex (HLA).

DIABETES MELLITUS is a common disease with obvious family clustering; yet the genetic mechanisms involved have not been well defined. Many genetic studies of diabetes have been hindered by the variability of expression in a family, by difficulties of definition, and by the many environmental factors that seem to influence the disease. One of the major obstacles has been the inability to determine the basic genetic defect involved in diabetes. The level of blood sugar is most likely several steps removed from the primary gene defect, and detection of the diabetic genotype prior to clinical manifestations is not possible. Diabetes does not appear to be the result of a single diabetes gene, but rather the expression of many different factors, both genetic and environmental, that determine blood sugar. In this paper we will review recent studies that shed light on the genetic factors which influence the expression of diabetes.

Genetic Heterogeneity of Diabetes

When the study of a disease with obvious genetic factors involved in its expression does not reveal a single genetic mechanism, genetic heterogeneity must be considered. Genetic heterogeneity implies that identical or similar phenotypes are the result of different genotypes. It now appears that diabetes mellitus is a genetically heterogeneous group of disorders. Clinically, adult-onset diabetes (AOD) and juvenile insulin-dependent diabetes (JIDD) behave differently, and family studies suggest that these are genetically distinct disorders. JIDD occurs more commonly in relatives of an individual with JIDD, whereas AOD occurs in these relatives at about the same rate as in the general population.[1] Although there is much overlap, JIDD and AOD tend to run true in a given family.

Twin studies also separate JIDD and AOD. Previous twin studies have shown that identical (monozygotic) twins have a higher concordance rate for diabetes than nonidentical (dizygotic) twins.[2] This has supported the view that genetic factors are involved in diabetes, but few of these previous studies have dealt with the different types of diabetes. In a current ongoing twin study in England 106 pairs of identical twins with at least one of the pair diabetic are being studied.[3] In this twin population, when the onset of diabetes is under 40, the concordance rate for both twins being diabetic is only 50%, and 50% of the twin pairs are discordant with only one twin in the pair diabetic. The concordance rate when the age of onset is over 40 is 93%, and it is 100% when the age of onset is over 50. This suggests that different genetic mechanisms are acting in AOD and JIDD, leading to the expression of three types of disease: (1) maturity-onset diabetes with a strong genetic component; (2) juvenile insulin-dependent diabetes with a strong genetic component, as in the concordant twin pairs; and (3) juvenile insulin-dependent diabetes with a strong environmental influence and a less significant genetic component, as in the discordant twin pairs.

One form of diabetes appears to have a distinct single gene pattern of inheritance that separates it from JIDD and AOD. This is the newly described maturity-onset type of hyperglycemia of the young (MOHY).[4,5] The diabetic phenotype in this condition is characteristic and different from JIDD. Those affected have postprandial hyperglycemia but have few of the long-term sequelae of other forms of diabetes. Hyperglycemia can be detected in the first two decades of life, but except for times of crisis, ketosis does not develop, and insulin therapy is not required. Family studies in MOHY show a pattern of autosomal dominant inheritance, with multiple generations affected and most of those affected having affected parents. The family history is the usual

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method of identifying this condition: Since the original description, it has not taken long to discover several large families with this condition in Minnesota.[6] The recognition of MOHY in the family is important to prevent unnecessary treatment of hyperglycemic children with insulin or other drugs. Since its prognosis seems so different from JIDD, it is best to avoid the term "diabetes" in regards to MOHY.

Immunogenetic Studies of Diabetes

Perhaps the most exciting and important of the recent studies of genetic mechanisms involved are those dealing with immunogenetic phenomena in diabetes. JIDD has now clearly been shown to have an association with the major histocompatibility complex (previously known as the HLA complex), and this association has defined a new approach for gaining insight into this complex disease. Before presenting the diabetes results, it is pertinent to review the genetics of the histocompatibility complex.

The major histocompatibility complex represents a cluster of four closely linked loci that control compatibility named A, B, C, and D. The major histocompatibility complex has been mapped to the short arm of chromosome 6,[7] and the relative position of the four loci on the chromosome is A---C-B---D. Although it is now officially called the major histocompatibility complex, the older term of HLA is commonly used to refer to this complex and will be used in this paper.

Antigens coded for by the A, B, and C loci are detected by serologic methods and are easiest to study. These three loci are very complex, with the A and B loci each having more than 20 alleles and the C locus having more than 5.[7] Antigens coded for by the D locus are detected by mixing lymphocytes from two individuals in culture and measuring the amount of cell stimulation that is the result of the different antigens on the cell surface. D testing is difficult. More than 10 alleles have been detected at the D locus.[8] The different alleles at each locus are referred to by a number preceded by the letter for that locus or a small *w* preceded by the letter. An example would be A1, B8 Cw3, Dw4. Most laboratories are only able to type for A and B antigens, and only a few are able to type for C and D antigens.

This complexity is simplified somewhat by the fact that any individual can have only one allele per locus on each number 6 chromosome. When an individual is typed for A and B antigens, it is possible to find either one or two antigens from each of these loci, signifying that two chromosomes carry the same or different alleles at each locus. The A and B alleles that are together on a given chromosome can be detected by family studies. For example, an individual can be shown to be positive for the A1, A3, B7, and B8 HLA antigens, but only after family studies can it be shown that the A1 and B8 are together on one chromosome and the A3 and B7 are together on the other, since the A1-B8 came from the mother and the A3-B7 from the father. The term haplotype is used to refer to the set of alleles for these loci that are together on a given chromosome. In the above example, the haplotypes are A1-B8 and A3-B7. Some haplotypes are more frequent in a population than expected from the frequency of the individual alleles, and this is thought to be related to a genetic advantage of certain combinations of alleles. Within a family haplotypes are inherited in a codominant fashion. If the father has haplotypes R and S and the mother has haplotypes P and Q, then the children can be RP, RQ, SP, or SQ. Siblings have a 50% chance of sharing one haplotype and a 25% chance of sharing two or no haplotypes.

Two types of studies have shown an association of JIDD and the HLA complex. The first deals with the difference in frequency of specific alleles in diabetic and non-diabetic populations. Nerup et al. in 1974 reported an increased frequency of HLA B8 and B15 alleles in JIDD patients.[9] Since then, a number of investigators have found an increased frequency of these two B locus alleles in JIDD patients.[10] The Dw3 allele is also associated with JIDD,[11,12] and it is likely that this finding is related to the increased frequency of B8. B8 and Dw3 are two alleles that are found together as a hapolotype in the population more frequently than expected, and there may be genetic selection for these two alleles being together in a haplotype.

The second type of study has been the analysis of HLA types in families with more than one diabetic member. Barbosa et al. studied 24 families with two or more individuals with JIDD in a sibship.[13] In these 24 families there was no significant increase in the frequency of B8, B15, or any other individual A or B allele, but there was an altered segregation of haplotypes. In each sibship, the diabetic siblings had the same haplotypes more frequently than expected from random segregation of parental haplotypes, with more than half of the diabetic siblings having the same two haplotypes. There appeared to be no clinical difference in the diabetes of those siblings sharing two and those sharing one haplotype. Linkage studies showed significant genetic linkage between the HLA complex and diabetes in these families, and suggested that the diabetes resulted from the effect of an autosomal recessive gene with a penetrance reduced to 50%.[13a]

Why is this association between HLA and JIDD present, and what does it tell us about the genetics of diabetes? Unfortunately, the specific answers to these questions are not known, but there are some very plausible suggestions that have been made. HLA alleles do not act directly as diabetes genes since the vast majority of the population with any of the alleles does not have diabetes. The relative risk as calculated for B8 and B15 is only 2.5 and 2.0 times the population frequency for individuals with these alleles, which is not a large increase in total risk. The best explanation for this association is that within the HLA region there are one or more genes that influence the development of diabetes rather than cause it directly. This gene is not part of the A, B, C, or D loci but rather is located on the chromosome between these loci, possibly between the B and D loci. It is close to, or tightly linked to, the B or D locus and so is indirectly detected when a diabetic individual is typed for B or D antigens. There is a precedent for this hypothesis in the mouse, which has the most extensively studied histocompatibility complex.[15] Mice have a number of genes called immune response (Ir) genes within the histocompatibility complex that control the animal's ability to respond to antigenic stimulation, and these Ir genes are located between the major loci that control the tissue antigens. The association of JIDD and HLA may be an indication of an Ir gene in man.

The HLA studies suggest that there is a diabetes response gene within the HLA complex that makes an individual susceptible to diabetes, and proper environmental stimuli will lead to the development of JIDD. The diabetes response gene may control susceptibility to particular viral infections, tissue localization with common viral infections, or immunologic response or lack of response to antigens. It may allow islet cell destruction and the development of JIDD. An individual may have a single (heterozygous) or a double (homozygous) dose of the diabetes response gene, and this difference would be expressed in a different type or degree of environmental stimulation required to produce the diabetic response. For example, a heterozygous individual might require a larger or a longer viral exposure than would a homozygous individual before developing diabetes. The homozygous individual would be more susceptible to the environmental stimuli, and, thus, more likely to develop diabetes. Once manifested however, the diabetes would be the same in the homozygous and heterozygous individual. Direct evidence for this mechanism is limited at the present time and must await future investigation.

Do HLA studies now have any place in the clinical management of families with diabetes? Typing an individual for HLA antigens adds nothing to the clinical program of diabetes management, but sibling and offspring typing does have a role in genetic counseling for JIDD.

Genetic Counseling in Diabetes

The knowledge that both genetic and environmental factors are involved in the etiology of diabetes should temper any tendency to be specific when providing genetic counseling for diabetes. It is usually not possible to know whether one is dealing with a type of diabetes that is mostly genetic or mostly environmental in nature.

The following common situations can be anticipated:

1. The juvenile insulin-dependent diabetic parent who wishes to know the risk to future children: Empirical data have shown that the risk to offspring is small, somewhere between one and 10%. If the parent developed the disease very early in life (before age 10), the risk is closer to 10%.
2. The non-diabetic parent with one diabetic child who wishes to know the risk to future children: In this case, the risk is also 1-10%.
3. The parents with maturity-onset hyperglycemia of the young who wish to know the risk to their offspring: This is an autosomal dominant condition and the risk is 50% for each offspring. The importance of recognition in this disease is the avoidance of unnecessary treatments. We also feel that these patients should not be labelled as diabetics, a term loaded with detrimental social connotations.
4. In those families with two or more first degree relatives with JIDD, HLA typing is useful in identifying family members at high risk for developing JIDD. This must be done in an established typing laboratory with complete sets of antigens to be exact.

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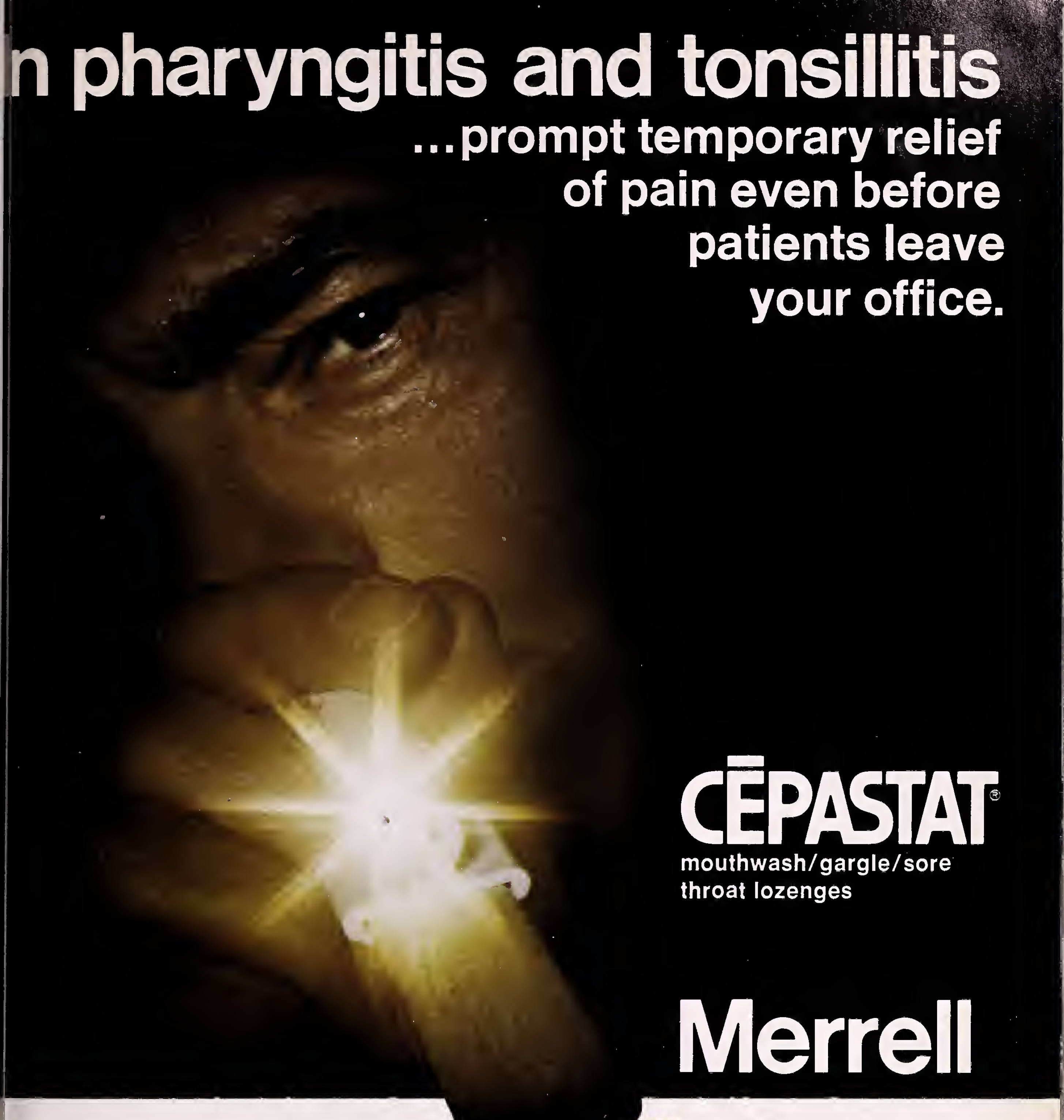
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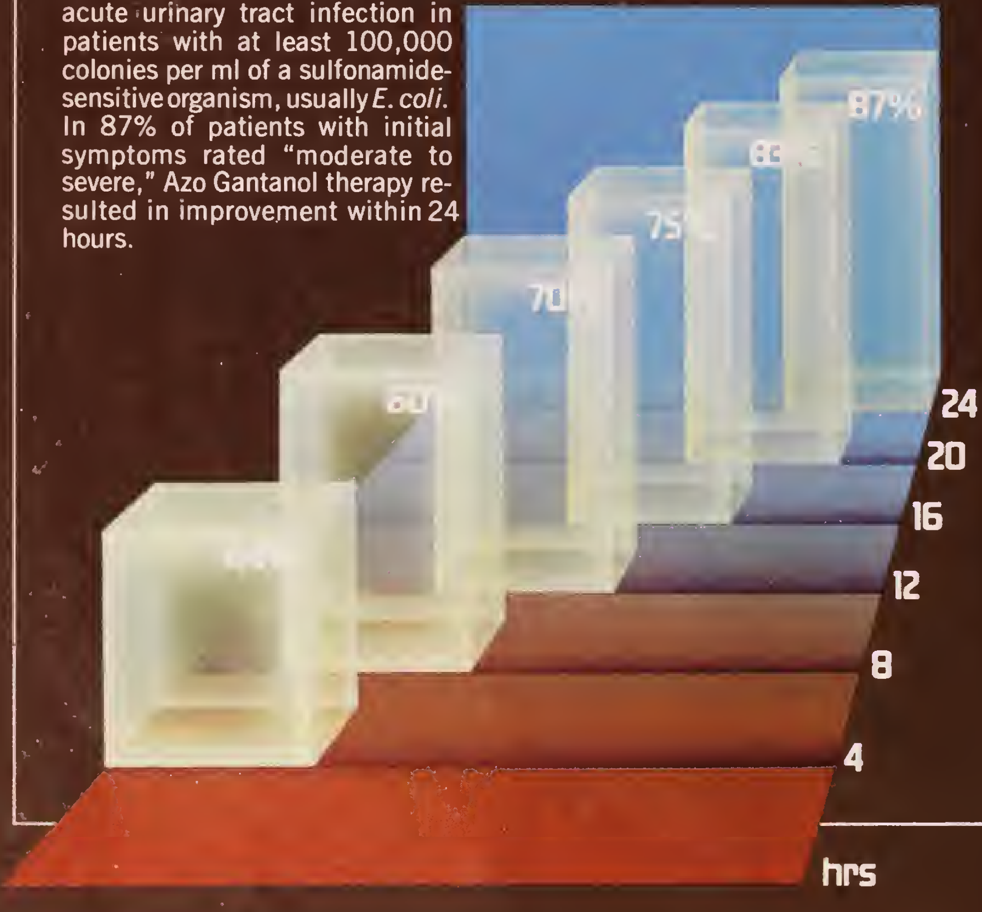

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neuritis, mental depression, convulsions,
hallucinations, tinnitus, vertigo and inso
miscellaneous reactions (drug fever, chills
nephrosis with oliguria and anuria, periar
nodosa and L. E. phenomenon). Due to
chemical similarities with some goitrogen
uretics (acetazolamide, thiazides) and ora
glycemic agents, sulfonamides have caus
instances of goiter production, diuresis a
glycemia. Cross-sensitivity with these age
exist.

Dosage: Azo Gantanol is intended for the
painful phase of urinary tract infections.
adult dosage: 2 Gm (4 tabs) initially, then
(2 tabs) B.I.D. for up to 3 days. If pain p
causes other than infection should be sou
After relief of pain has been obtained,
treatment with Gantanol (sulfamethoxazo
be considered.

NOTE: Patients should be told that the o
dye (phenazopyridine HCl) will color the

Supplied: Tablets, red, film-coated, each
ing 0.5 Gm sulfamethoxazole and 100 mg
phenazopyridine HCl—bottles of 100 and

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Obesity and Diabetes Mellitus

FRANK Q. NUTTALL, M.D., PH.D.*

The most common type of diabetes mellitus is that associated with obesity. If dietary treatment fails, treatment with either oral hypoglycemic agents or insulin is indicated.

OBESITY IS THE single most common form of malnutrition in the United States. Statistics available from the U.S. Public Health Service indicate that 25 to 45 percent of the adult American population over age 30 are overweight. In children the incidence of obesity is two to 15 percent.[1] Overall it has been estimated that the United States population is five billion pounds overweight.

There is a limit to the amount of carbohydrate and protein that can be stored in the body, but there appears to be no limit to the amount of fat that can be stored. Persons weighing 500-600 pounds are well known. In the past, this ability to store fat when food was plentiful undoubtedly had survival value since it would allow a person to survive a period of famine. Also, in the northern climate, an individual might gorge himself in summer, much as bears do, in order to be able to exist in a state of starvation or semistarvation over the winter months. A normally proportioned 70 kg man has only enough stored fuel to last for a maximum of three months provided all available fuel is completely utilized.[2] A 150 kg obese man has sufficient stored fuel to last for approximately fourteen months. Thus, in a severe famine, the latter person would have a much better chance of survival. That man can survive extended periods of starvation has been demonstrated many times. The record in the literature is an obese lady who tolerated over eight months of complete starvation with minimal side effects.[3] This would be impossible for a normal weight person. The survival value related to storage of large amounts of fat probably is the reason this genetic trait is still so prevalent in the general population in spite of a cultural bias against it.

In addition to its being culturally undesirable, it is clear that in our society obesity also no longer is a physiologically desirable trait. Epidemiologic[4] and life insurance actuarial data indicate that obesity is associated with a shortened life expectancy.[1,5] This excess mortality for the most part is not due to the obesity per se but rather to abnormalities associated with obesity. Two major abnormalities associated with obesity and known to increase mortality are hypertension and diabetes mellitus.[4–7]

The frequent association of diabetes mellitus with obesity has been known for centuries. Indian doctors of the sixteenth century A.D. considered it a disease of the rich and greedy and used fasting as an effective therapy.[8] In the United States and Western Europe diabetes associated with obesity is the single most common type of diabetes. It is estimated that 65 to 80 percent of adult-onset diabetics are obese.[9] The increasing prevalence of diabetes in the United States also may be due to the increasing prevalence of obesity in our society.

Even though an association of diabetes with obesity has been known for a very long time, factors relating the two remain unknown. It is clear that obesity precedes the onset of diabetes, usually by many years, and the duration rather than the severity of obesity correlates best with the development of diabetes.[8,10] Often a rather sudden increase in obesity is noted one or two years before the onset of overt diabetes. This has been clearly documented in the Pima Indian study.[11]

Family studies strongly suggest a genetic basis for the obesity associated type of diabetes. Obese subjects are three times as likely to have diabetic parents as are normal weight healthy persons. Also obesity without diabetes has been reported to be three times as frequent in families of diabetic persons.[7,8] Of some interest is a report that the prevalence of diabetes correlates with the distribution of the excess fat mass, being more common in those individuals with most of the fat in the truncal and upper body areas (Android type).[12]

Several abnormalities in fuel metabolism have been noted in obese individuals. These most likely are effects of the obesity per se and not the cause of obesity, since they appear in normal thin individuals in whom obesity is induced by overfeeding.[13] These abnormalities include an increase in serum cholesterol and triglycerides and an increase in serum insulin concentration both in the fasting state and during a glucose tolerance test. The insulin concentration in the fasting state and after glucose administration has been shown to be directly correlated with the severity of obesity.[14] In spite of the grossly elevated circulating insulin concentrations, glucose tolerance is normal or even slightly impaired. This indicates that in obese persons insulin is less effective in lowering the blood glucose than in normal thin persons. That is, they have "insulin resistance." An impaired ability of insulin to stimulate glucose transfer into muscle cells also has been demonstrated directly using insulin infusions into a forearm artery.[15] In addition, a reduced ability of insulin to inhibit amino acid release from muscle[16] and to inhibit release of fatty acids from adipose tissue[15] has been demonstrated in obese subjects. Thus the resistance to insulin affects the metabolism of all types of fuel.

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The mechanism of insulin resistance induced by an increased fat mass is unknown. However, it may in part be due to so called "down regulation" of insulin receptors. A chronic elevation of circulating insulin from any cause reduces the number of insulin receptors on the surface of insulin sensitive cells.[17] Since obesity is characterized by an elevation in circulating insulin, this could explain the insulin resistance if the observed reduction in cell surface receptors can be shown to lead to an impaired metabolic response to insulin. There is considerable research in this area at the present time, and answers should be forthcoming.

Obese individuals eating the same diet as at normal weight subjects secrete three times as much insulin in a twenty-four hour period.[18] With the development of diabetes, the capacity to produce these large amounts of insulin is impaired. Because of the presence of insulin resistance, however, glucose tolerance becomes abnormal even when the insulin levels are similar to those in normal, thin persons. If the obese person at this stage of diabetes can return to a normal weight, glucose tolerance may return completely to normal since the resistance to insulin is lost.[15,17,19] If the obese person cannot reduce his adipose mass significantly, then a mild diabetes will persist. With time, the diabetes will become more severe as the ability to secrete insulin is further impaired. These observations have led to the concept of beta cell exhaustion, i.e., the constant excessive demand for insulin production eventually leads to a state where the beta cells no longer can maintain such a large output, and they begin to fail. Whether this is true, or whether there is a basic genetic abnormality in the beta cells independent of the obesity which results in functional failure as the person ages, is uncertain at present. Since obese persons require more insulin to maintain normal fuel metabolism, there is little question that the onset of diabetes could be delayed if a normal body fat mass is maintained. Only rarely do patients with this type of diabetes lose the ability to secrete insulin completely and become the truly insulin-dependent, ketosis-prone type of diabetics.

Treatment

The best treatment for the obese patient with diabetes is weight reduction. With return to a normal body weight, mild diabetes may disappear completely. With more severe disease, there generally will be improvement, and treatment by other means will be easier. As a rule of thumb, a fasting plasma glucose of 200 mg/100 ml or greater indicates the ability to secrete insulin is severely limited, and a complete normalization of glucose concentration with weight reduction is unlikely.

Most obese individuals can reduce and many even attain an ideal body weight. However, regardless of the weight maintenance program recommended, few are able to maintain an ideal body weight for an extended period of time.[20] The physician should strongly encourage the obese patient to lose weight and maintain the weight reduction. Strong psychological support also should be offered to the patient in his efforts to maintain an ideal weight. However, unless the patient is highly motivated, little success can be anticipated. Failure to meet the expectations of the physician often leads to guilt on the part of the patient and frustration of or rejection by the physician. In this climate, neither the patient nor the physician are likely to maintain an interest in treatment of the diabetes. Certainly good medical care never should be withheld from an obese patient merely because the patient is unable to lose weight.

In my opinion, many obese persons have a genetic abnormality in either appetite regulation or in regulation of body fat mass. It is only with a continuing conscientious effort that they are able to maintain a reasonably normal body weight, an effort that most physicians would find impossible to accomplish themselves. Failure in maintenance of a normal body weight then is to be expected and must be understood and accepted by the physician.

Treatment of the diabetes in obese patients who are unable to lose weight or maintain a normal weight poses a problem for which there is not a clear solution. In the Pima Indian study[11] diabetic retinopathy appeared when the fasting or two hour postprandial plasma glucose concentration exceeded 200 mg/100 ml; therefore, we have advocated treatment to keep the plasma glucose below this level at all times. In mild diabetics complete normalization of the plasma glucose should be the goal. If this can be accomplished by weight reduction or by a low carbohydrate diet, no further treatment is necessary. If not, we advocate small doses of an intermediate acting insulin (NPH or Lente). Usually a single morning injection will suffice, but in some cases an additional injection before dinner may be necessary. Ordinarily this is about one-third of the morning dose. Addition of short acting insulin (Regular) to the intermediate acting insulin in the morning dose also sometimes helps to obtain better control. If the patient is less than forty years of age and there is no evidence of cardiovascular disease, oral hypoglycemic agents may be tried initially, provided good control can be obtained.

There is considerable concern that insulin therapy or the oral hypoglycemic agents will stimulate the appetite and as a result cause a greater increase in obesity. Certainly in animals large doses of insulin can lead to obesity,[21] and insulin treatment of malnourished diabetic patients leads to dramatic weight gain. However, exacerbation of existing obesity has not been documented in diabetic humans. Indeed, the weight of patients attending a large diabetes clinic was found to be amazingly stable regardless of the type of treatment used. In this study the majority of the patients were of the obese, adult-onset type of diabetic.[22]

Since obese patients rarely die from the obesity per se but rather from associated complications, particularly atherosclerosis, diabetes and hypertension, it is logical to focus on prevention or treatment of these abnormalities. It still is not certain that excellent control of the diabetes will prevent the long term complications of the disease and prolong life. However, evidence is accumulating which suggests that this is, indeed, the case.[23] Thus, a vigorous effort to normalize the plasma glucose should be made in each patient. This is best accomplished by caloric restriction and weight reduction. However, if this is unsuccessful, other conventional treatment should not be withheld merely because the patient is and will remain obese.

Summary

The most common type of diabetes mellitus is that associated with obesity. This type of diabetes is associated with insulin resistance as well as an impaired ability to secrete insulin. The best treatment is weight reduction and maintenance of a normal body fat mass. This often leads to complete normalization of plasma glucose values. As with any other diabetic patient, however, if dietary treatment fails, treatment with either oral hypoglycemic agents or insulin is indicated.

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Minnesota Chapter, American College of Surgeons
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Ocular Changes in Diabetes

HOWARD D. GILBERT, M.D.*

Ocular changes significantly affect the status of diabetic patients. Diabetic retinopathy, a potentially blinding disease, is the most serious ocular complication. Current modes of therapy have improved the prognosis for this disorder, making recognition and appropriate evaluation of diabetic retinopathy important from a sight saving point of view. Rubeosis iridis, lens changes, and ocular muscle palsies also are associated with diabetes mellitus.

DIABETES MELLITUS is a complex systemic disease which may cause marked changes in the eye. The most important of these changes are diabetic retinopathy, rubeosis iridis, lens changes, and ocular muscle abnormalities, and these are the subject of this review.

Diabetic Retinopathy

Diabetic retinopathy is by far the most important of the ocular changes in diabetes. It is the leading cause of new adult blindness in this country in persons less than 60 years of age. Fifty percent of all diabetic patients have some evidence of retinopathy after ten years of diabetes, and more than 80% show retinal changes by twenty five years.[1] Diabetic retinopathy is divided into two major classifications, background diabetic retinopathy (BDR), and proliferative diabetic retinopathy (PDR). Overall, approximately 15% of all patients seen with background retinopathy will be legally blind in five years.[2] Patients with proliferative retinopathy have a much worse prognosis. From the natural history of this disease, one-half of these patients will be legally blind in the involved eye in five years or less.[3] About ten percent of diabetics develop this type of retinopathy. From this data, it is apparent that retinopathy is both a common and severe problem among diabetic patients.

As is well known, diabetes mellitus is associated with small blood vessel disease everywhere in the body, and the retina of the eye is no exception. The common factor in the development of all stages of diabetic retinopathy is thought to be retinal ischemia. The subsequent alterations in capillary permeability and the development of microaneurysms are the earliest signs seen clinically in background diabetic retinopathy. Microaneurysms are dilatations 75-100 microns in size which occur predominantly on the venous side of the retinal capillaries. They may form and then disappear at a later time. Punctate retinal hemorrhages often occur concomitantly with the microaneurysms (Figure 1). This type of pathology is primarily located at the posterior pole of the eye temporal to the macula, and is easily seen with the direct ophthalmoscope. Microaneurysms are abnormally permeable allowing transudation of intravascular fluids. Components of this fluid form the hard, sharply-defined, yellow-white exudates seen in background diabetic retinopathy. These are more common and often more extensive in older patients. Often they appear in a ring formation with a group of aneurysms in the center, and are termed circinate

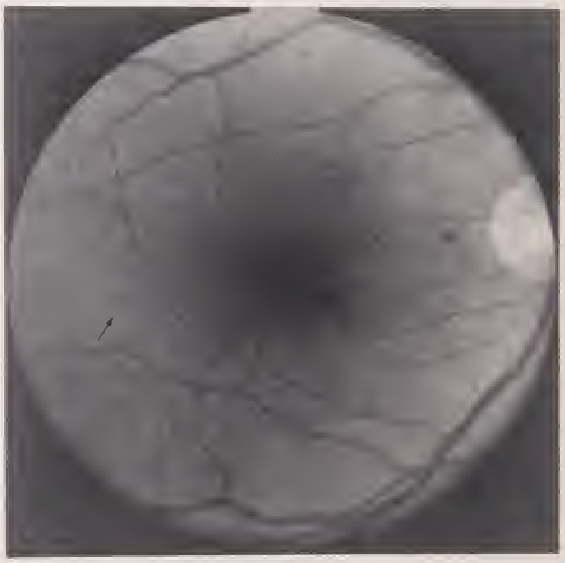

Fig. 1 — Early background diabetic retinopathy. Visual acuity is 20/20. Punctate hemorrhages lie inferior to the macula, and scattered microaneurysms are present (arrow).

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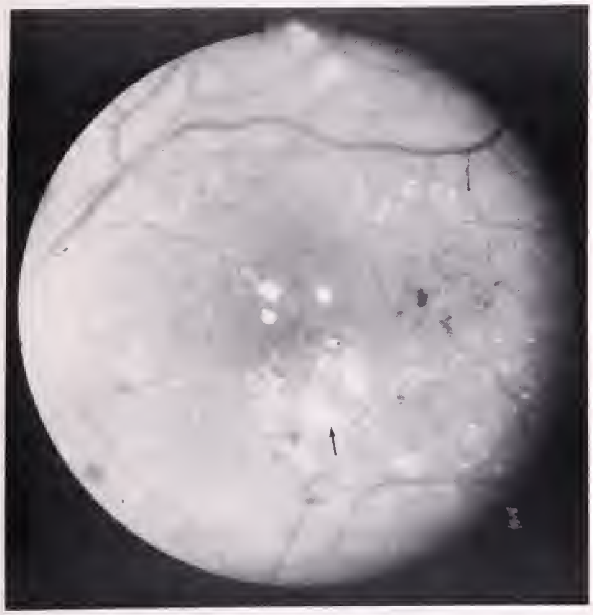

Fig. 2 — Background diabetic retinopathy with severe macular edema. The hard exudates (arrow) are indicative of long standing transudation of fluid.

retinopathy. Hard exudates, like the microaneurysms with which they are associated, appear in the posterior pole of the eye and may come and go with time.

With the continued transudation of fluid from retinal microaneurysms, retinal edema develops. When this edema involves the macula, visual acuity is reduced. This macular edema is the most common cause of persistent decreased vision in diabetic patients (Figures 2, 3). Cystic spaces centered like petals form in the macula and are visible with the ophthalmoscope, but are better seen with the slitlamp or by fluorescein angiography. The severity of the edema may wax and wane, but the natural history is for a gradual progressive decrease in vision.

More aggressive background retinopathy may lead to additional abnormalities. Intraretinal microvascular abnormalities (IRMA) are shunt vessels contained within the retina which are usually adjacent to the areas of occluded capillaries. They are evidence of ischemia (Figure 4). Soft exudates or cotton-wool spots representing infarcts in the nerve fiber layer of the retina, are also evidence of progressive ischemia and advancing retinopathy. They are ¼ to ½ disc diameters in size and are more faint than those seen in hypertension. Usually, they disappear in a few months time, and they tend to decrease markedly in number if proliferative retinopathy develops. Venous abnormalities, such as dilatation or beading, often accompany soft exudates. These are caused by abnormalities in blood flow on the venous side of the capillaries and

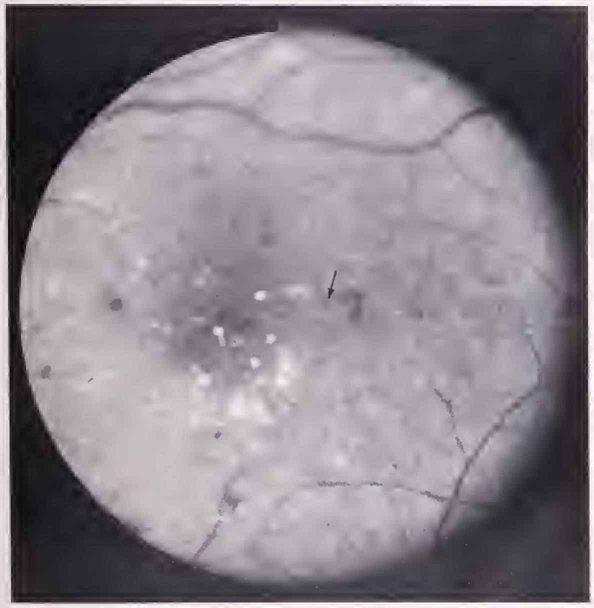

Fig. 3 — Same eye as Figure 2 three months after photocoagulation therapy. Note the marked reduction in the hard exudates. The arrow shows a photocoagulation scar.

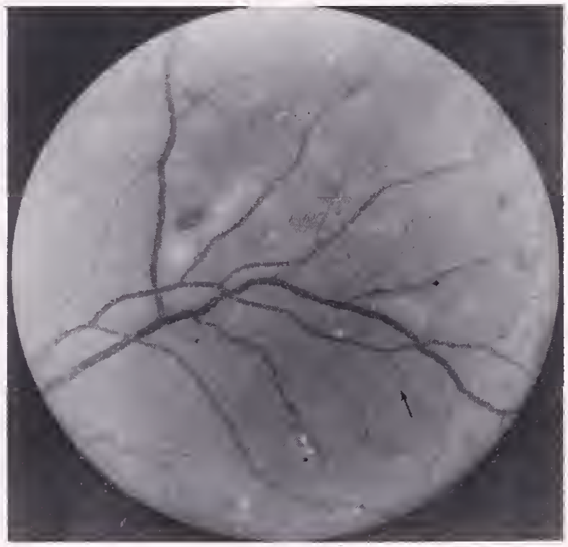

Fig. 4 — Preproliferative retinopathy. The triad of soft exudates, venous irregularities, and IRMA (arrow) are demonstrated in this single photographic field.

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in the small venules upstream from where the changes are grossly visible. The initial observable stage is venous dilatation, which may progress to irregularities in caliber, beading, and then to actual venous loops. Neovascularization often develops later in these same areas. When IRMA, cotton-wool spots, and venous abnormalities occur together in a diabetic patient, the condition is termed preproliferative retinopathy. At this stage, the chances are excellent that the patient will develop proliferative retinopathy within a year. Patients with these abnormalities should be followed very carefully every few months for changes in their retinopathy.

The onset of proliferative diabetic retinopathy is heralded by the development of neovascularization in the retina. These new vessels typically occur on or near the optic disc (NVD), (Figure 5). They may also occur elsewhere in the retina (NVE), typically along the vascular arcades and temporal to the macula. In these locations, they are nearly always adjacent to areas of capillary closure. Initially, these neovascular fronds appear "bare", although histopathologically they do have fibrous or glial supporting tissue. With further fibro-glial proliferation along the new vessels, adhesions to the vitreous humor become more prominent. The fibrous tissue thickens and shortens with time causing traction on the vessels and elevation of the vessels into the vitreous. Vitreous hemorrhage often occurs with sudden catastrophic loss of vision. Traction or rhegmatogneous retinal detachments may also develop. In the "burned out" or "involutional" state, no further hemorrhage occurs, but one is left with an ischemic retina and the other anatomic alterations which have already occurred during the course of the proliferative disease.

This natural course of proliferative retinopathy may stop spontaneously at any stage, just as is true of background retinopathy. However, proliferative retinopathy tends to be more malignant and progressive. Overall, nearly 20% of eyes with untreated proliferative retinopathy have less than 5/200 visual acuity two years later, primarily due to vitreous hemorrhage and/or traction retinal detachment.

Treatment of diabetic retinopathy has come to the attention of the medical community over the past five years primarily as a result of the development and general availability of the argon laser. At the present time, laser photocoagulation is known to be of benefit in treating both macular edema and proliferative retinopathy[4,5].

The treatment of macular edema involves focal photocoagulation to leaking microaneurysms near the macula. If these can be destroyed without making the macula too ischemic, edema fluid may cease to accumulate (Figures 2, 3). The residual fluid may disappear and the vision improve (25%) or stabilize (50%). In about 25% of patients, the treatment is not beneficial. Long standing edema, marked central

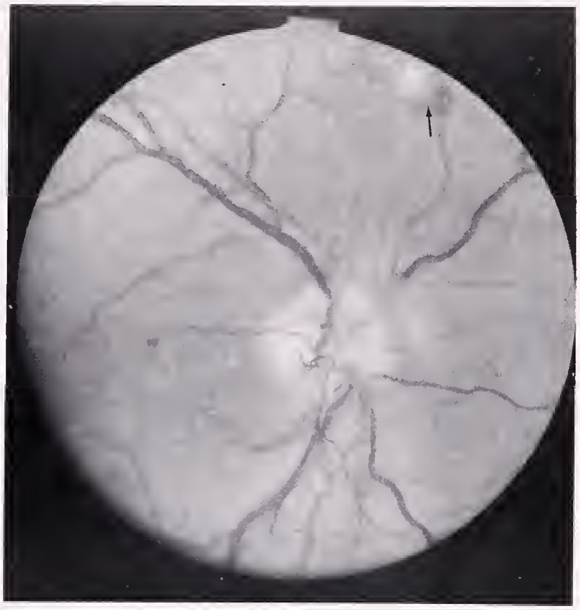


Fig. 5 — Proliferative diabetic retinopathy. Both disc neovascularization (NVD) and an area of neovascularization elsewhere (NVE) are shown (arrow).

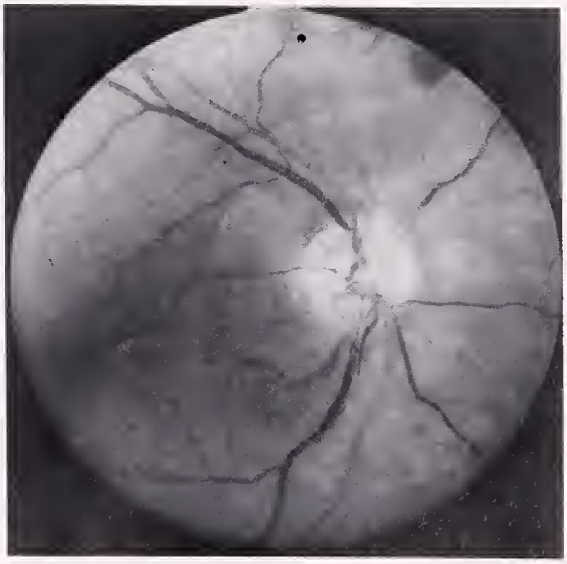


Fig. 6 — Proliferative diabetic retinopathy. Same eye as Figure 5 two months after pan-retinal photocoagulation with the argon laser. Note the marked resolution of new vessels on the optic nerve head.

ischemia, and hard exudates in the center of the macula are poor prognostic signs.

Treatment of proliferative retinopathy by pan-retinal photocoagulation (PRP) has been proved beyond a doubt to be beneficial by the recent collaborative study[5] (Figures 5, 6). The goal of treatment is to prevent vitreous hemorrhage, thereby, preserving vision. The procedure involves placing approximately 1500 laser burns in a scatter fashion throughout the ocular fundus sparing only a two to three disc diameter area around the macula. After almost three years of the study, nearly 30% of the group of untreated eyes had vision of less than 5/200, as compared to only 10% of the treatment group. This data is very significant when one considers this was a prospective collaborative study of 1700 patients where each subject had one eye randomly selected for treatment, and the other eye followed as a control. Photocoagulative therapy therefore should be considered in patients with background retinopathy with macular edema (vision less than 20/40), and in patients with any proliferative diabetic retinopathy.

Patients who go on to nonclearing vitreous hemorrhage, and/or tractional retinal detachment may now be helped in some cases. The development of techniques for closed vitrectomy has enabled surgeons to work inside the eye to remove blood and scar tissue from the vitreous cavity, to treat traction retinal detachments, and in some cases to remove membranes from the retina[6]. Sixty percent of patients with these problems can be helped, while only ten years ago, no therapy was possible in these cases.

Rubeosis Iridis

Rubeosis iridis is the development of new blood vessels on the anterior surface of the iris. These vessels are most prominent at the pupillary margin and usually begin there. They may grow more peripherally on the iris. When the vessels involve the anterior chamber angle, glaucoma is invariably associated, and recurrent hyphema is common. The glaucoma is extremely difficult to manage, both medically and surgically. These eyes often progress to become blind and painful in a short time and may require enucleation. The condition is most often associated with severe retinopathy. There is now some early evidence that rubeosis iridis also responds favorably to pan-retinal photocoagulation, such as that applied for proliferative retinopathy.

Lens Changes

Variations in diabetic control with their concomitant fluctuations in blood glucose cause marked changes in the refractive power of the eye. As the blood glucose rises, the eye becomes more myopic; as it falls, the eyes becomes more hyperopic. The shifts in serum osmolality and blood glucose alter the fluid balance of the lens, and thereby change its refractive power. When the patient's condition stabilizes, the refractive power also stabilizes, and visual acuity again becomes constant.

Cataract development is associated with diabetes. These cataracts develop earlier and more rapidly than the typical senile cataract. Young diabetics are especially susceptible. The opacity consists of many white punctate dots, flakes, and vacuoles in the lens cortex just beneath the anterior and posterior lens capsule. When vision is significantly reduced, cataract operation can be performed just as for senile cataract.

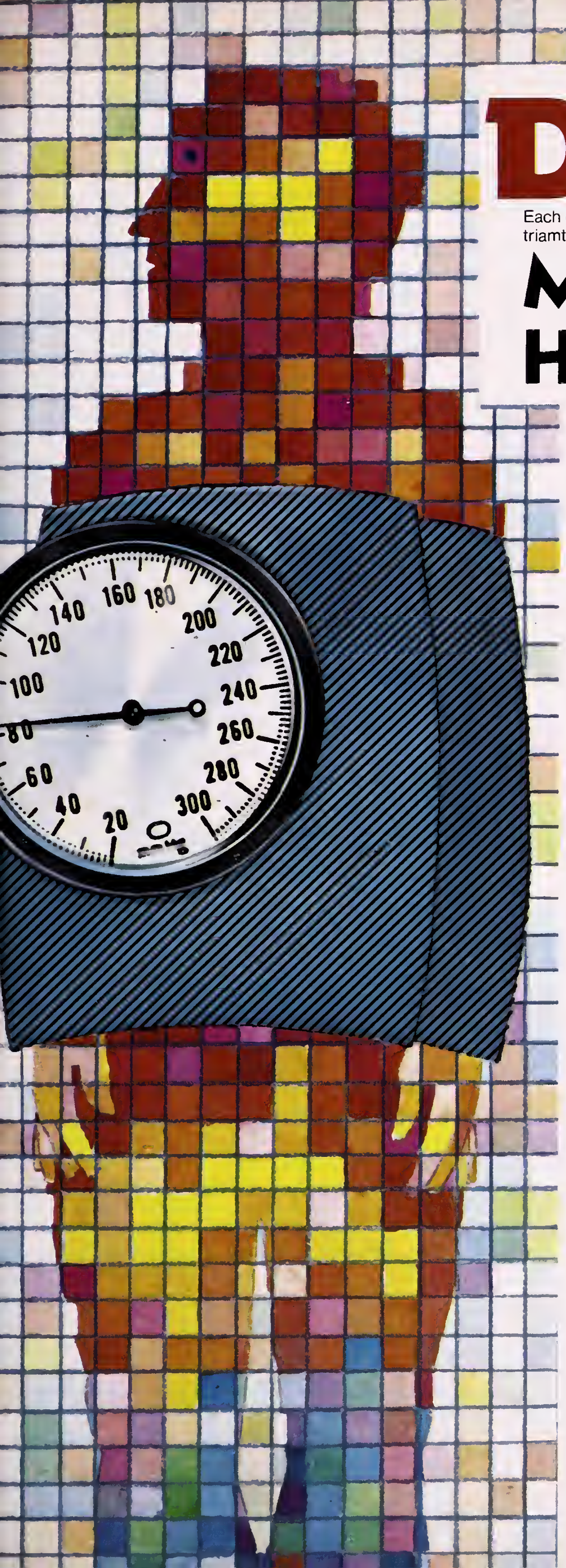
Ocular Muscle Abnormalities

Oculomotor abnormalities occur in about 1% of diabetic patients. They tend to occur in older diabetics and are unrelated to the severity of the disease. They may be the presenting sign of diabetes. Most commonly, the third or sixth nerve is involved. The fourth nerve is only rarely affected. The onset of palsy is sudden and may be associated with severe pain or homolateral headache. When the third nerve is involved, the pupil is nearly always spared, which helps to differentiate this from an intracranial aneurysm. Recovery occurs almost universally over a period of weeks to a few months. As a rule, aberrant regeneration does not occur. The pathogenesis of this condition is not understood, but most likely is of a vascular nature. In evaluating diabetic patients who develop typical sixth or third nerve palsy with pupillary sparing, only a skull film is ordered. Recovery is expected. If there is no history of diabetes, a glucose tolerance test is ordered. According to Walsh, if this is negative, it is repeated after giving moderate doses of steroids. If the test is then positive, recovery still is expected[7].

Summary

The great majority of diabetic patients develop ocular complications of their disease. The lens changes and ocular muscle abnormalities are quite manageable problems. Rubeosis iridis is much more difficult, and diabetic retinopathy remains the biggest challenge of all. With recent advances in its management, the importance of careful evaluation is critical, and should be an ongoing part of the diabetic's care.

References will be found on page 45.



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Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

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Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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Pylorospasm has almost totally blocked passage of barium meal.

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"The correlation of spasm relief and drug given was excellent."

[*] This drug has been classified "probably" effective in treating certain functional G.I. disorders.

[†] See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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For use as adjunctive therapy in the treatment of peptic ulcer.
IT SHOULD BE NOTED AT THIS POINT IN TIME THAT THERE IS A LACK OF CONCURRENCE AS TO THE VALUE OF ANTICHOLINERGICS/ANTISPASMODICS IN THE TREATMENT OF GASTRIC ULCER. IT HAS NOT BEEN SHOWN CONCLUSIVELY WHETHER ANTICHOLINERGIC/ANTISPASMODIC DRUGS AID IN THE HEALING OF A PEPTIC ULCER, DECREASE THE RATE OF RECURRENCES, OR PREVENT COMPLICATION

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

May also be useful in the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis, acute enterocolitis, and functional gastrointestinal disorders); and in neurogenic bowel disturbances (including the splenic flexure syndrome and neurogenic colon).

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

- For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug PRECAUTIONS. Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy Use with caution in patients with: autonomic neuropathy; hepatic or renal disease; ulcerative colitis—Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon; hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension; hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.
It should be noted that the use of anticholinergic/antispasmodic drugs in the treatment of gastric ulcer may produce a delay in gastric emptying time and may complicate such therapy (antral stasis). Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia, urinary hesitancy and retention; blurred vision and tachycardia, palpitations; mydriasis; cycloplegia; increased ocular tension, loss of taste, headache; nervousness; drowsiness; weakness, dizziness; insomnia; nausea; vomiting; impotence, suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION Dosage must be adjusted to individual patient's needs.
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Insulin Therapy

Things That Make a Difference

G. E. COTTON, M.D.* AND A. J. SILL, M.D.†

Blood glucose levels can, by skillful use of insulin, be maintained at more optimal levels than is often the case. Patient education, multiple daily injections of insulin, proper timing of insulin action, small and infrequent changes in insulin dosage, routine use of regular insulin, injection of insulin into the abdomen if exercise is anticipated, avoidance of Somogyi effect, and dilution of insulin to U-25 or U-50 with dosage changes of ¼ to ½ unit in those patients who are extremely sensitive to insulin action are all of considerable importance. The emotional status of the patient should always be considered if control is difficult.

Consider adrenal, thyroid, pituitary or renal insufficiency in patients with decreasing insulin requirements.

Insulin lipoatrophy and insulin allergy are briefly discussed.

Obese, non-ketotic, adult onset diabetics are often not candidates for insulin therapy.

THOUSANDS OF INSULIN-requiring diabetics follow a prescribed insulin regimen quite carefully but, nevertheless, remain hyperglycemic most of the time. In the vast majority of these patients considerable normalization of the blood glucose can be attained and maintained without producing an unacceptable amount of hypoglycemia. One of the critical factors in achieving this improved control is optimal use of insulin. Some factors in the use of insulin found to be helpful in improved control of diabetes are the subject of this paper. Emphasis is on day-to-day chronic management of diabetes. Much of the material presented is of anecdotal nature, representing impressions gained from a large referral practice of diabetology and seven years experience in patient education in a diabetes education center.

Patient Education

Diabetes mellitus is a disease which is treated by the patient. The physician's role is primarily to see that the patient is properly educated. Nowhere is this concept more important than in the use of insulin. The patient must be able to make adjustments in his insulin treatment regimen with essentially the same facility as the physician. Obviously an occasional patient will not be able to handle this task, but the vast majority can learn to do so very nicely. The physician should not give up on his slow learners, and he will be amazed at how well they do. Out-patient diabetic education programs are readily available at several well established centers‡

A treatment protocol must be followed that is easily learned and readily understood by the patient. One such regimen has been previously described in this journal.[1] This program may be compromised if motivational, physical or mental handicaps exist.

Number of Insulin Injections

Very few diabetic patients can be controlled as well with a single injection of insulin daily as with two or more injections. Also the incidence and severity of hypoglycemic episodes are decreased with multiple injection programs. With a single injection of an intermediate acting insulin, patients are allowed to be hyperglycemic throughout most of the day in order to avoid unacceptable hypoglycemia in midafternoon. Such a regimen should be reserved for patients with compromised situations as mentioned above. Patient acceptance of a multiple injection regimen is excellent; physicians are more reluctant.

A plan of insulin therapy using a mixture of regular and an intermediate-acting insulin was described in this journal in November, 1976.[1] This regimen consists of 50% regular and 50% NPH insulin mixed in the same syringe. Two-thirds of the daily dose is given 20-30 minutes before breakfast and one-third 20-30 minutes before supper. Adjustments in the basic program are made to match the patient's diet and exercise patterns as well as patterns of glycosuria. Similar alternative programs also have been published.[2] Easily learned by patients, the resulting self-adjustment in insulin dosage leads to freedom from glycosuria in many patients in whom this is not obtainable with a single daily injection of insulin. Hypoglycemic reactions are infrequent and mild.

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Alternative multiple injection programs likely will provide improved control, but should follow a protocol easily learned by the patient, and specific guidelines for patient adjustment of insulin dosage should be provided.

Timing of Insulin Action

In the non-diabetic, a constant baseline secretion of insulin occurs, with additional insulin provided specifically when needed; i.e. at time of meals. Normally, insulin is secreted in response to the sight and smell and ingestion of a meal.[3] Furthermore, "early" or prompt insulin secretion may well occur in response to hormones liberated from the gastrointestinal tract, such as gastric inhibitory polypeptide released from the gastric mucosa and known to stimulate the acute release of insulin.[4–6] This potential role of the gastrointestinal tract in regulating early insulin secretion has given rise to the concept of the entero-beta cell axis. It is believed that insulin is normally "there and waiting" for glucose to be absorbed, or at the least, the presence of the two is precisely matched.[42] Later, the rising blood glucose level becomes, itself, a stimulus to further insulin secretion. Insulin given by injection should attempt to simulate normal physiology as closely as possible. Peak insulin activity should match peak postprandial glucose levels and there should, ideally, be some increase in insulin activity in anticipation of the rise in blood glucose associated with eating. Routine use of regular insulin before breakfast and before supper helps considerably in achieving this optimal timing of insulin action.

Increment and Frequency of Change of Insulin Dosage

Perhaps the most frequent error in routine, day-to-day management of the diabetic patient involves insulin increments which are too large and changed too frequently. In the absence of ketosis, elevated blood glucose levels should be gently nudged back towards normal rather than pushed by making large or frequent changes in insulin dosage. In the newly diagnosed diabetic four injections of regular insulin alone are given 20-30 minutes before each of four small meals,[2] the total amount approximating 2 units/Kg per day. After three to four days an estimate of insulin requirements can be made with reasonable accuracy. Thereafter mixed intermediate and rapid acting insulin are given in a split dose. Reductions are made as needed when remission ("honeymoon period") occurs, but small doses are continued throughout the remission period.

In subsequent management, two rules are essential. First, changes in insulin dosage should be small — one, or at the most, two units (occasionally less in children) at a time. Secondly, changes in insulin dosage generally need not be made except every two or three days until stable control is acquired. Such changes may be made over and over again until the desired effect is attained. Once optimal control is attained, continued monitoring and additional adjustments should be made as necessary, to compensate for fluctuations in blood glucose and/or ketosis that may occur from time to time, such as with exercise, menstrual periods, surgery or other stress. Many diabetics require two to three months to reach best obtainable control. Gradual changes avoid hypoglycemic reactions and resulting Somogyi effects. Long-term control is greatly improved by the educated patient being able to make adjustments when needed, not merely at time of physician contact. Also, because the basis of adjustment of insulin dosage is careful monitoring of urinary glucose and occasional blood glucose measurements using Dextrostix, such informed patients are more motivated and better appreciate the value of testing their urine and blood glucose on a routine basis and more frequently when problems arise.

During illness or stress increments of insulin and frequency of dosage change will necessarily be much greater, especially in adults. Five to twenty unit increments may be needed if ketosis is present. Multiple doses of regular insulin (five-10 units every two-four hours) may be required temporarily until the illness is controlled or the stressful situation alleviated.

Role of Regular Insulin

Regular insulin is not only the keystone of management in any compromised or crisis situation in diabetes; it is an absolute requirement for optimal control in day-to-day management of many adult diabetics and all young diabetics. When included in the treatment regimen with intermediate acting insulin, it improves control in all but the mildest, most easily managed diabetics. Recommendations for the portion of regular insulin used varies from 30 to 50% of the total dose.[2,1,7] A general rule, however, is that patients on a split dose generally require two thirds of their regular insulin in the morning. It is important to realize that these percentages merely represent estimates of a starting point. Adjustments are made as necessary in the individual case.

Neutral regular insulin can be mixed with NPH or Lente insulin in the same syringe. Each will retain its individual time-action properties.

Extreme Sensitivity to Insulin

Rarely a diabetic patient, especially a small child, may be so sensitive to the effects of insulin that a single unit increase in dosage results in hypoglycemia; and a decrease of one unit severe hyperglycemia, or even ketoacidosis. These patients usually have no endogenous secretion of insulin. Their total insulin supply must be provided by injection. Perhaps the most difficult of all insulin-requiring diabetics to treat, it is seldom that average blood glucose levels can be kept at or near the normal range without producing an unacceptable number of hypoglycemic episodes. Clearly such patients must be on a split dose of insulin, intermediate and regular insulin before breakfast and before supper. The optimal proportions of each must be discovered by experience in the individual case but, in general, a 2/3-1/3 division proves useful. Rarely, regular insulin alone, in three or four injections, must be used. A single injection of insulin, regardless of type, will never provide adequate control for these insulin deprived unstable diabetics. Furthermore, once puberty supervenes, ketosis as much as hypoglycemia may be as difficult or even more of a problem.

In these very insulin sensitive patients, insulin often must be diluted so that accurate measurements of one-fourth or one-half unit may be made. Changes of one-fourth to one-half unit every three or four days may be needed to seek out the best obtainable control. U-100 insulin can be diluted to U-25 or U-50 using a special dilutant available from the manufacturer.

Effect of Exercise on Insulin Absorption

Glucose is used for fuel during exercise, but neither non-diabetics, nor diabetics given insulin by constant intravenous infusion, have a drop in blood glucose during moderate exercise. Diabetics given insulin by subcutaneous injection, however, are prone to hypoglycemia during moderate exercise.[25] This is due to decreased glucose production,[25] probably due to the fact that insulin is absorbed from a depot site more rapidly during exercise. This effect is most marked if the injection is made into the thigh and the leg is exercised. Studies by Koivisto & Felig,[8-9] during leg exercise by bicycle have shown 135% exercise induced increase in absorption in the first 15 minutes, and this remains 50% greater at 60 minutes when the injection is made into the thigh. No increase was noted when the injection was made into the abdomen, and absorption was reduced in the post exercise period. No change at either time was noted when the injection was made into the arm. It is obvious that the exercising patient should, if possible, inject insulin into the abdominal wall or arm on days when vigorous exercise is anticipated. Data is not available in regard to exercised arms. If exercise is to involve the arms, it may be prudent to inject into the abdominal wall. If unexpected exercise occurs after insulin has been injected into the thigh, provision of extra calories prior to the exercise is important. In all patients with recurrent hypoglycemic reactions, an exercise history must be carefully evaluated.

Insulin Allergy and Insulin Resistance

A major treatise of insulin allergy is beyond the scope of this article. More detailed coverage is available in several recent articles.[10-13] Local reactions such as slight redness and itching around the injection site are common and are especially likely to occur if insulin therapy has been temporarily interrupted and then resumed. Usually these manifestations disappear with continued use of insulin. Systemic reactions with urticaria, pruritis and angioneurotic edema are IgE mediated. Anaphylactic reactions to insulin are rare[23] but more likely to occur in atopic individuals, and when insulin has been interrupted and then resumed. Desensitization using minute quantities of monospecies insulin (usually pork) is required in patients who demonstrate bona fide allergy to insulin.

When insulin antibodies (IgG) are responsible for severe insulin resistance, use of pure pork monocomponent regular insulin may (often in large increments hourly) result in correction of the problem, but use of altered insulin, e.g. dealaninated pork insulin may be required. If these measures are unsuccessful, high dose glucocorticoid therapy must be instituted (80-100 mg./day prednisone in divided doses) to stop further antigen-antibody coupling and to enhance dissociation of existing complexes.[14]

It should be stressed that unless a clinical problem suggests insulin allergy there is no known advantage to using pure pork insulin or other monospecies insulin on a routine basis. These products are of limited availability, and the usual mixture of beef and pork insulin is quite satisfactory for the majority of patients.

Emotions and Insulin Requirements

It must be emphasized that most childhood, adolescent and adult insulin-requiring diabetics are easily kept between the extremes of hypoglycemia on one hand and ketoacidosis on the other. Nevertheless, occasionally a teenager, young child or young adult rather abruptly becomes extremely difficult to control. Wide fluctuations of blood glucose and/or ketosis may occur for no obvious reason. Under these circumstances the patient's family and social relationships and situational circumstances must be thoroughly explored. Frequently profound emotional problems will be discovered.

That the effects of emotions on glucose metabolism are profound and dramatic is well known to diabetologists.[15-16] The case of an 18 year old easily controlled diabetic comes to mind.[24] This young man, diabetic since the age of 13, developed severe ketoacidosis for the first time within 3 hours after witnessing the death of a friend in a motorcycle accident, even though he himself was untouched — a dramatic illustration of how stress, either physical or emotional, can precipitate acute ketosis and even ketoacidosis. In young diabetic patients with difficult problems in adjustment and coping, counseling and psychotherapy, especially with involvement of an understanding family, can be of considerable benefit in establishing stable control.

Decreasing Insulin Requirements

Several causes of decreasing insulin requirements are known, but none is more important than adrenocortical insufficiency. Adrenal failure occurs in association with a number of endocrine abnormalities, but the most common association is with diabetes mellitus.[17-20] This diagnosis should be considered whenever insulin requirements drop and hypoglycemic reactions become a problem, especially when there is a family history of autoimmune endocrine deficiency states such as idiopathic hypoparathyroidism, adrenocortical insufficiency or Hashimoto's thyroiditis with or without hypothyroidism. One of us, (GEC), has recently reviewed the record of a 12-year-old diabetic female who died from hypoglycemia and adrenal insufficiency. This patient last presented to our hospital with a history of increasing frequency of hypoglycemic reactions, decreasing insulin requirements, hyperkalemia, some degree of leukopenia with lymphocytosis and eosinophilia. Her post-mortem examination showed near complete destruction of the adrenal cortises.

Renal insufficiency is a second cause of decreasing insulin requirements. Once documented, treatment of chronic renal insufficiency should be instituted and insulin dosage adjusted accordingly.

Additional autoimmune diseases which may be responsible for decreased insulin requirements include such entities as primary hypothyroidism and hypopituitarism, which are known to occur with increased frequency in patients with diabetes mellitus.

Somogyi Effect

Perhaps the single most common problem in diabetic patients who are said to be difficult to control or "brittle" is the occurrence of frequent Somogyi effects. "Post-hypoglycemic hyperglycemia" is responsible for wide glycemic excursions, and until the hypoglycemia is prevented for two or three days, return of insulin sensitivity with reduction in rebound hyperglycemia is not possible. In these patients, hypoglycemia is followed by increased gluconeogenesis in the liver and elevated hepatic glycogenolysis with resultant hyperglycemia. Furthermore, the stress of hypoglycemia in susceptible patients leads to catecholamine-induced acceleration of lipolysis with increased hepatic ketone body production.

Classically the Somogyi effect has been attributed to insulin antagonism, possibly due in part to glucagon mediated epinephrine release. At any rate, hypoglycemic reactions *always* indicate the need for reduction in insulin dosage. An extremely elevated blood glucose on the morning following a hypoglycemic episode in the preceding several hours does not obviate this need. The reduction can be made at a rate of one, two, four or occasionally more units daily until the hypoglycemic episodes cease. After three or four days of freedom from hypoglycemic reactions, the dose should be very slowly adjusted upward until optimal control is attained, short of producing further hypoglycemic reactions.

Insulin Lipoatrophy

Children and adolescent girls are more prone to subcutaneous loss of adipose tissue at the sites of insulin injection.[26] A benign condition, its significance lies in the emotional reactions resulting from cosmetic disfigurement. Probably due in large part to immune (allergic) phenomenon,[27-28] lipoatrophy is seen more commonly with use of the less pure insulins which often contain undesirable high molecular weight materials.[29-30]

Treatment consists of injecting highly purified insulin into the involved site, or the use of sites other than the lipoatrophic areas. In a series of 300 patients reported by Wentworth, et al.,[31] 80% improved with use of mixed beef-pork "single peak" insulin. [All regularly available commercial insulin is now "single peak".] Many of the remainder will respond to single peak pure pork insulin. Virtually 100% of patients will respond to injection of single component pork insulin (the purest insulin currently available), but this should be reserved for those who do not respond to the more readily available forms.

Early in treatment the affected area will have a "doughy" consistency, and two to four weeks are needed for normal tissue to develop. Once normality is restored, "maintenance" injections every two to four weeks are needed to prevent re-excavation. Too frequent injections, however, will lead to insulin hypertrophy.

Insulin lipoatrophy will not respond to treatment if co-existing local allergy to insulin is present until the allergy is treated effectively. Only then will local insulin injection be effective.

When Not to Use Insulin

Obese patients with or without diabetes, and non-obese patients with untreated maturity onset diabetes have altered insulin sensitivity. This alteration is a non-antibody related insulin resistance resulting in a decreased response of the target tissues to insulin.[32,33] This type of insulin resistance is also frequently seen in Cushing's syndrome, acromegaly, myotonic dystrophy and in patients taking corticosteroids or oral contraceptives. In most cases, plasma insulin levels are elevated after an overnight fast.[34-35]

Insulin secretory dynamics in non-diabetic obese and in diabetic obese and non-obese patients have been quite well defined.[34-37] In general obese people have higher insulin levels than non-obese people both fasting and after glucose loading.[35] Prior to development of hyperglycemia, obese subjects show an exaggeration of both early (first phase) and the more gradual second phase of insulin secretion.[37] Hyperglycemia develops when the early phase of insulin secretion becomes impaired.[36] The second, or late phase may remain intact. The cause of insulin resistance in obesity and maturity onset diabetes has not been fully clarified. However, insulin receptors on the membranes of target cells are reduced in number and in their affinity for the insulin molecule in both conditions.[32,38,39] This undoubtedly plays some role, but probably does not totally explain the insulin resistant state. In obesity, the receptor alterations are reversible, returning toward normal with weight reduction. Antibodies to insulin receptors have been reported as a cause of insulin resistance in patients with acanthosis nigricans.[40]

Average daily peripheral insulin delivery has been studied by Genuth.[21] He reported that lean adult non-diabetics deliver 31 units per day; massively obese non-diabetics 114 units per day. Juvenile diabetics deliver four units per day, lean adult onset diabetics 14 units per day and obese adult onset diabetics 46 units per day.

Ninety percent of adult onset diabetics are obese, but they are only rarely ketosis prone. Obesity influences the degree of peripheral insulin resistance, the magnitude of insulin delivered peripherally, and the timing of insulin secretion. While the values for peripheral insulin delivery reported by Genuth[21] may be too low (more frequent sampling resulted in higher values[41]), the ratios are certainly accurate. Thus deficiency of the total amount of insulin delivered peripherally is not the major problem in obese adult onset diabetics.

In our experience insulin therapy is relatively ineffective in obese non-ketosis prone adult onset diabetes. Stimulation of appetite by insulin may result in increased food intake and further obesity. Increased obesity leads to further insulin resistance and perpetuation of the hyperglycemic state. The large dose insulin therapy often given to this type of patient thus not only fails to correct the hyperglycemia but actually aggravates the situation. Many such patients when initially seen are taking 100 or more units of insulin daily. Discontinuation of insulin and calorie restriction in a controlled setting usually results in a decrease in blood glucose levels within 2-3 days. The decrease in blood glucose towards normal is progressive and parallels weight reduction. Interim use of oral hypoglycemic agents during the weight reduction phase of treatment may normalize the blood glucose. When ideal weight is reached, a weight maintenance diet is prescribed, and the oral hypoglycemic agent is discontinued. Return of hyperglycemia despite adequate weight control is best managed by reinstituting therapy with an oral hypoglycemic agent, or alternatively, with low-dose insulin therapy. As the obesity has been corrected, insulin sensitivity will have returned and insulin therapy will be effective.

Dietary therapy and weight reduction are the primary and only truly effective forms of management in obese non-ketotic, adult onset diabetes mellitus. However, patient compliance with recommended dietary therapy has been disappointing and a source of frustration to both patients and physicians. To be successful, the dietary prescription must in many cases be incorporated into a total behavior modification program. It must be stressed that in the absence of calorie restriction and weight reduction, fully adequate treatment does not exist for the obese, non-ketotic, adult onset diabetic.

Summary

A number of factors relating to the clinical use of insulin are important in optimal management of insulinopenic diabetes mellitus. Patient education is essential. Multiple injections of insulin each day (usually with a combination of regular and an intermediate acting insulin), insulin action at time of glucose presence, self-adjustment of insulin dosage by the patient (using small, infrequent changes), liberal use of regular insulin, attention to sites of injection as related to exercise, emotional factors and the Somogyi effect are all important in routine daily management of diabetes with insulin. Special problems including extreme sensitivity to insulin, insulin allergy, lipoatrophy, and decreasing insulin requirements are discussed. Insulin therapy should be avoided in most obese, non-ketotic, adult onset diabetics.

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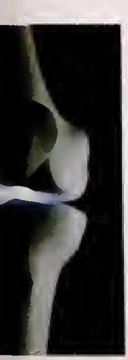

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Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

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Nutritional Management in Diabetes

MARION FRANZ, R.D., M.S.*

Nutritional management is essential if the goal of attaining optimal blood glucose levels is to be achieved. The nutritional goals for the insulin dependent diabetic differ significantly from the goals for the non-insulin dependent diabetic. Mechanics of nutritional management involve knowledge of: (1) carbohydrate, protein, and fat metabolism; (2) distribution, size, and timing of food intake; (3) formulation of prescriptions; (4) caloric requirements; (5) adjustments for exercise, delay of meals, illness, use of alcohol, and pregnancy requirements.

A MAJOR GOAL in the treatment of diabetes is the optimal regulation of glucose levels. One of the goals of therapy should be to achieve levels of blood glucose as close to those in the non-diabetic as feasible.[1] Nutritional management is a crucial means of achieving this goal. Quality nutritional care includes development of an appropriate individualized diet prescription and on-going nutritional education and counseling. It is essential to convey to the patient an understanding of both the goals and the mechanics of nutritional management.

Goals of Nutritional Management

The goals of nutritional management for the insulin dependent diabetic differ from the goals for the non-insulin dependent diabetic. Frequently these differences are not fully appreciated. Nutritional management must take into account the specific goals related to the type of diabetes.

Insulin-Dependent Diabetic

The first goal is to prevent the acute complications of hypoglycemia and hyperglycemia and their consequences. This involves a proper balance of food, insulin, and usual patterns of exercise. Timing of meals and snacks should be consistent from day to day. Feedings must be planned to avoid long spans between meals. In the regulation of blood glucose levels, consistency and predictability of food intake is more important than proscription of any specific food items.

The second goal of nutritional management is to provide for normal growth rates in children and attainment and maintenance of desirable body weight in adults. Periodically the child's pattern of growth with reference to height and weight should be recorded on a growth chart, such as the one developed by the National Center for Health Statistics. (Figure). If there is a change in height or weight, as shown in the case in the Figure, assessment of the control of diabetes and/or the need for additional calories should be made. The adult insulin dependent individual also needs periodic assessment of weight. Desirable body weight should be maintained.

The third goal is the prevention or delay of the long-term complications associated with diabetes.

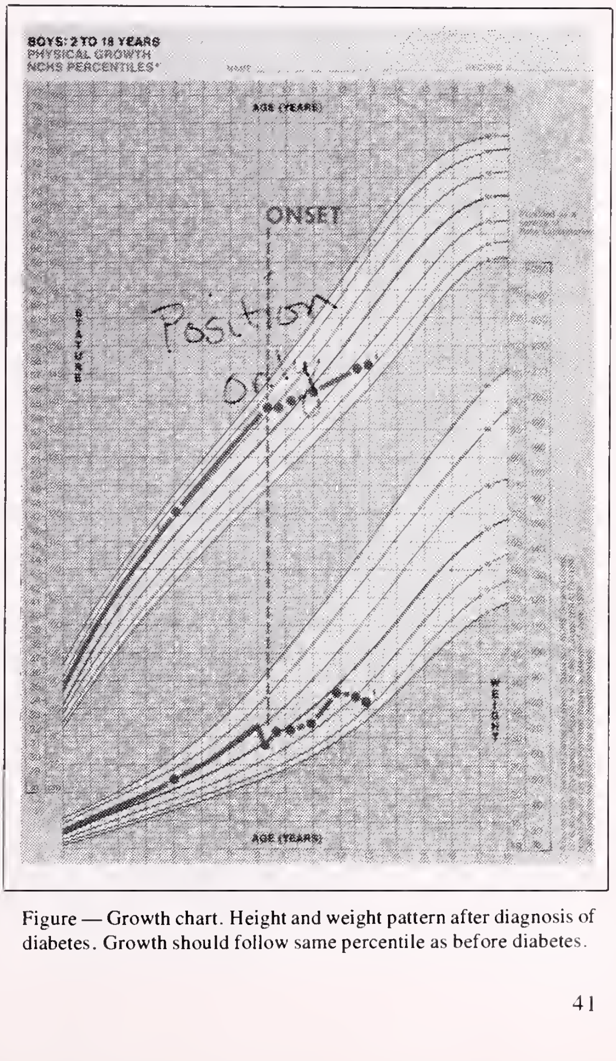

Figure — Growth chart. Height and weight pattern after diagnosis of diabetes. Growth should follow same percentile as before diabetes.

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*Director of Nutrition, St. Louis Park Medical Center and Diabetes Education Center, Minneapolis, Minnesota.

Epidemiologic evidence suggests that prevention and control of hyperglycemia can prevent and/or mitigate microvascular lesions. Thus, diet modification has great potential for preventing and controlling not only diabetes but also certain of its complications.[2]

The fourth goal is to attain and maintain optimal nutritional status. Every nutritional management plan should provide for an adequate supply of all essential nutrients. The meal plan for the individual with diabetes can be an excellent nutritional guideline for the entire family.

Non-Insulin Dependent Diabetic

The National Commission on Diabetes in 1975 reported that 70% of the maturity-onset diabetics in the United States were above desirable body weight at the time of diagnosis. The chance of becoming diabetic doubles for every 20% an individual is above desirable body weight. This is in extreme contrast to individuals with insulin dependent diabetes who are usually underweight at diagnosis. Nearly all of these overweight diabetics produce enough endogenous insulin to maintain normal blood glucose levels if they are able to reduce to desirable weight. In this type of diabetes the prime objective is caloric restriction, irrespective of the source of calories. Reduction in adiposity improves sensitivity to insulin and usually improves glucose tolerance.[2] Since these individuals usually do not require exogenous insulin, timing of meals and regulation of distribution of nutrients is not crucial. However, those persons requiring oral hypoglycemic agents may experience hypoglycemia if meals are skipped.

The most frequent acute concern in the non-insulin dependent person is hyperglycemia. Frequently within days of initiating a low calorie diet, elevated glucose levels will show a remarkable decrease towards normal. Hyperglycemia can be prevented with a restricted calorie diet and/or increased exercise pattern. Control of hyperglycemia often lowers serum cholesterol levels, while regularly and substantially lowering serum triglycerides.[2]

Often non-insulin dependent diabetes is diagnosed after the initial progression of a chronic complication. Modification in meal planning may be necessary for hypertension, hyperlipidemias, cardiovascular problems and renal insufficiency.

As with the insulin-dependent diabetic, the fourth goal is to attain and maintain optimal nutritional status. Unless the calorie level is less than 1,200 calories, the meal plan can be nutritionally adequate. At lower caloric levels, vitamin supplementation may be necessary.

The increasing body of evidence suggests that hyperglycemia needs to be controlled. With this emphasis so called "free diets", particularly in children, have fallen into disfavor. Diet modifications that aid in control of hyperglycemia have been shown to have favorable effects on growth rates in children and favorable effects on serum lipids and glucose tolerance in adults.[2]

Mechanics of Diet Therapy

In the planning of meals for individuals with diabetes the primary concern will be with carbohydrate, protein and fat, since these three nutrients supply energy (calories) and require insulin for their metabolism.

Carbohydrate, Protein, Fat

Approximately 50% of the total calories in the meal plan should be derived from carbohydrate, mainly starch. There is no need to restrict disproportionately the intake of carbohydrates in the diet. Increase of dietary carbohydrates, even to extremes, without increase of total calories, does not appear to increase insulin requirement.[3] Insulin need is more closely related to total caloric intake than to carbohydrate intake. One of the reasons is the excellent capability of the diabetic liver to manufacture glucose from a variety of noncarbohydrate sources. In the non-insulin dependent individual, substitution of carbohydrates for fat does not elevate fasting blood glucose, worsen glucose tolerance, or elevate triglyceride levels.[2]

The use of refined sugars is discouraged and the use of starches and complex carbohydrates is encouraged. Sugars tend to produce sharp elevations of the blood glucose, while high starch diets are very well tolerated if caloric intake is appropriately controlled.[4]

The mistaken notion that "diabetic diets" are necessarily expensive is based largely on the outmoded concept that starch is bad for diabetics and must be replaced with more expensive foods, such as meat and dairy products.

It is desirable to derive approximately 20 percent of the total calories from protein. Proteins are the building blocks of the body but also serve as a secondary source of energy. Through the process of gluconeogenesis 50 to 60 percent of the protein molecule has the potential to yield glucose.

Approximately 30 to 35 percent of the total calories should be derived from fat. Dietary fat does not have an immediate effect on blood sugar levels, but needs to be taken into consideration for two reasons: (1) A gram of fat supplies nine calories, whereas carbohydrates and protein supply only four calories per gram. Foods high in fat, therefore, are high in calories. (2) Restriction of food high in saturated fat, and substitutions with foods that contain polyunsaturated fats is recommended wherever feasible. There are favorable effects of a high starch, low fat diet on both serum cholesterol and triglyceride levels and prognosis for development of vascular disease.[2]

Exchange Lists

Knowing we are concerned about the carbohydrate, protein and fat content of foods, we next need to translate this into terms the patients can easily use for food selection. The most widely used system is the Exchange Lists for Meal Planning[5], which was developed by the American Diabetes Association and the American Dietetic Association in the 1950s and most recently revised in 1976. Other equally effective management programs have been developed, but exchange lists have achieved nation-wide acceptance. Many patients are already familiar with their basic concepts.

The exchange system divides food into six lists. Each list contains food items that are similar in calories, carbohydrate, protein and fat content. Therefore, a food item on a given list can be exchanged or substituted for any other item on the same list. Purposes of the recent revision were: (1) promotion of greater accuracy and awareness of the caloric values of food; (2) modification of the fat content of the diet with emphasis on foods low in total fat content and low in saturated fats; and (3) provision of greater flexibility in individualized meal planning. .

Distribution of Food Intake

A meal plan states how many servings the individual should select from each list at each meal and at snack times. A meal plan is designed taking into account the individual's nutritional needs and lifestyle, the level of endogenous insulin, and normal patterns of physical activity for the individual patient. Within any particular daily calorie allotment, the amounts of the various nutrients may be distributed in many ways among the various meals and snacks.

In the insulin-dependent patient, consistency of timing and distribution of food intake is important, but there is usually some flexibility in determining the distribution pattern to be followed. Such adjustments are made possible by the substantial number of available alternatives with respect to insulin therapy. For example, a person who prefers a small breakfast may receive a smaller dose of short-acting insulin before breakfast or even no rapidly acting insulin at this time. A person who prefers or needs a larger breakfast may be given a larger dose of short-acting insulin. Consistency of food intake, therefore, is the most important factor.

Most insulin dependent patients do best with three meals and three or four daily snacks. Regular ingestion of a mid-afternoon snack often facilitates a better fit with the time action curves of the intermediate acting insulins, such as NPH or Lente. A morning snack is usually necessary when short-acting insulins, such as Regular or Semi-Lente insulins are used. Some children do best with four snacks, two being afternoon snacks. A bedtime snack is important for all insulin-dependent diabetics to give protection from hypoglycemia during the night hours. Of prime importance is that these feedings be predictable in their size, timing and general characteristics. Persons on oral hypoglycemic agents may also require afternoon and evening snacks. Individuals on diet alone may be treated with three meals and three snacks or with only three prescribed meals, depending on their ability to control food intake.

Developing a meal plan that is reasonably consistent with the patient's preferences and situation greatly increases the likelihood that it will be followed. A slightly suboptimal but well followed prescription is usually preferable to a theoretically ideal prescription that is unattractive or unfeasible[2].

Formulating the Prescription

The best way to start is to find out what, where, and how much the patient would eat if he did not have diabetes. It is desirable in determining the prescription to give as much consideration as possible to the patient's own preferences with respect to kinds of foods and eating schedules.

Requirements of the diabetic diet usually allow considerable flexibility in deciding the proportions of carbohydrate, protein and fat to be prescribed for any individual. It is therefore almost always possible to construct a prescription and meal plan that is attractive as well as appropriate. Modify the patient's diet only to the degree necessary to meet the truly essential requirements imposed by the diabetes.

A complete diet history provides the basis for developing a meal plan most suited to the individual's needs and lifestyle. Using information gained, meal plans usually can be adapted to suit the patient thereby making changes on the part of the patient as minimal as possible.

Calorie Requirements

The individual's calorie needs are based on desirable body weight and activity levels. It is not urgent that a precise determination be made initially of the levels of calories to be prescribed. An estimate can be made with appropriate adjustments subsequently on the basis of experience[2]. Dietary objectives in the lean, insulin-dependent diabetic are regulation and consistency of distribution, not proscription and deprivation.

Children under 15 years of age require an average of 1,000 calories plus 100 calories per year of age. Thus, a seven-year old child would require roughly 1700 calories per day. Because size and activity levels vary considerably in children of the same age, the formula should be used only as a crude guideline. All too frequently inadequate calories are prescribed for the juvenile diabetic.

In lean patients an initial prescription that is generous helps to make the point that the main objective is regulation rather than deprivation. Satiety, appetite and hunger are usually reliable guides to the caloric requirements, but body weight is the definitive long-term guide.

For the non-insulin dependent diabetic, diets too low in calories cannot be realistically followed for any length of time. Diets in the range of 1300 to 1500 calories for women and 1500 to 1800 calories for men promote better compliance and allow for gradual weight loss.

Evaluate and alter meal plans as necessary according to patient's acceptance. In children, it is important to monitor growth and to make sure that calories are adequate. In adults it is important to monitor weight gain or loss and make appropriate changes.

Exercise, Illness, Alcohol, Pregnancy

The need to treat food items imaginatively and to adjust continuously to the vagaries of exercise, illness or work schedules suggests that the term "dietary regulation" fits the appropriate regimen better than terms such as "rigid diet" or "strict diet".

All insulin dependent patients should be instructed regarding the need for extra food to balance episodes of unusual exercise. Extensive exercise that is not habitually performed usually requires 10-50 grams of extra carbohydrate. Moderate exercise requires 10-15 gms. of extra carbohydrate per hour while vigorous exercise may require 20-30 grams of extra carbohydrate per hour.

When meals must be delayed, ingestion of 15-30 grams of carbohydrate protects from hypoglycemia for one to two hours.

When illness curbs appetite in insulin-dependent patients, special measures are required. Consumption of carbohydrate in any form at the rate of 50 grams per meal missed or every three to four hours usually suffices to prevent the ketosis of starvation. The lessening of insulin requirement which attends diminished calorie intake is at least balanced by an increase in requirements induced by illness. Small frequent carbohydrate feedings are desirable as protection against ketosis and hypoglycemia[6].

Alcohol is high in calories (7 cal/gm.) and devoid of nutritional value, except as a source of calories. In fasting, insulin-dependent patients, alcohol can cause hypoglycemia which may not be recognized if symptoms are attributed to intoxication. Many alcoholic drinks, i.e., beer and sweet wines, also contain appreciable amounts of carbohydrate. Alcohol tends to promote hypertriglyceridemia. Patients using oral hypoglycemic agents may experience symptoms of flushing, nausea and quickened heart beat after drinking. Excessive intake of alcohol appears to interfere in some way with normal peripheral glucose utilization even though adequate insulin is available.

Even so, in most patients an occasional drink can be permitted. In individuals where weight is a concern, a convenient method is to trade fat calories for alcohol calories. In the normal weight individual whose diabetes is well controlled, moderate use of carbohydrate-free alcohol (two ounces) may be regarded as an "extra."[7]

During pregnancy it is necessary for the mother who has diabetes to maintain careful control of the diabetes. The diet must take into account not only the metabolic requirements of the mother, but also the developing fetus. A total weight gain of 22 to 28 pounds is recommended with the pattern of weight gain more important than the total amount. Pregnancy is not a time for weight reduction.

Caloric requirements can be met by the addition of 300 calories per day to the pre-pregnancy meal plan. Fifty grams of carbohydrate and 30 grams of protein should supply the additional calories. The diet should contain approximately 1800 to 2500 calories a day. The importance of regular meals and snacks must be emphasized. In particular, the bedtime snack is essential because of the tendency towards overnight hypoglycemia and ketosis.[11]

Summary

Goals of nutritional management for the insulin-dependent diabetic include: (1) promotion of normal blood glucose levels to prevent the acute complications of diabetes by balancing food, insulin, and exercise; (2) providing for normal growth rates in children and desirable body weights in adults; (3) good control of the diabetes to prevent or delay long term complications; (4) a nutritionally adequate diet. Goals for the non-insulin dependent diabetic include: (1) attainment and maintenance of desirable body weight; (2)

prevention of hyperglycemia; (3) modifications necessary for long-term problems; and (4) a nutritionally adequate diet.

When the character of the meals and snacks are well suited to the patient's tastes and schedules they are more likely to become an acceptable habit and therefore a dependable element of the therapeutic program.

Day-to-day adherence to a meal plan takes strong motivation on the part of the individual with diabetes. It is essential that the individual have proper education, followup, and support from all members of the health care team. Hopefully, then the goals of nutritional management can be realized.

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Potential Future Modes of Therapy in Diabetes Mellitus

JOHN E. GERICH, M.D.*

Recent evidence strongly suggests that the long-term complications of diabetes are mainly the results of insulin deficiency; because current modes of controlling hyperglycemia in the diabetic are inadequate, new methods to improve insulin delivery or insulin action are being sought. These and other potential new future treatment modalities are reviewed here.

Considerable evidence recently has accumulated in favor of metabolic factors as major determinants of the onset and progression of the so-called "long-term complications" of diabetes. This may be briefly summarized as follows: nephropathy, retinopathy, and neuropathy similar to that found in idiopathic diabetes occur both in patients who develop "secondary" diabetes (hemochromatosis/pancreatectomy)[1-3] and in animals made diabetic experimentally.[4-6] Capillary basement membrane thickening, the hallmark of diabetic microangiopathy, develops sometime *after* the onset of diabetes and increases with the duration of the disease.[7-9] Moreover, monozygotic twins discordant for diabetes have discordant muscle capillary basement widths — the twin without diabetes having normal basement membranes.[10] In animals made diabetic experimentally, cure of diabetes by pancreatic transplantation or meticulous control of hyperglycemia with insulin prevents or minimizes the formation of diabetic lesions in the eye, kidney, and nerve.[6,11-14] Finally, both in man and certain animals, kidneys transplanted from normal donors into diabetic recipients develop histologic lesions characteristic of diabetes;[15,16] and, at least in the rat, kidneys taken from diabetics and transplanted into normal recipients show disappearance or lack or progression of diabetic lesions.[15,17] These findings suggest that in man appropriate correction of insulin deficiency will prevent or diminish the long-term complications of diabetes.

Insulin lack causes numerous metabolic derangements in a variety of tissues; the most blatant manifestation is glucose intolerance. Because hyperglycemia is easily monitored, control of diabetes is usually expressed in terms of circulating glucose levels or glycosuria. It is generally assumed, but by no means established, that the restoration of normoglycemia also reflects correction of other metabolic consequences of insulin lack. In nondiabetic individuals, blood glucose levels vary little throughout the day — rarely exceeding 160 mg/dl even after meals.[18] Unfortunately, most studies indicate that the beneficial effects of control of hyperglycemia in diabetes require meticulous regulation of plasma glucose to levels approaching those seen in nondiabetic individuals.[6,11-14] Because this is not possible with current modes of treatment, an intensive search for better methods is underway. These and other potential areas susceptible to therapeutic intervention are the subject of this review.

Improvement of Insulin Delivery

Although work continues on agents which act directly on pancreatic B cells to augment residual insulin secretion (e.g. oral hypoglycemic agents), major emphasis has been placed upon the transplantation of tissue containing B cells (e.g. islets, whole pancreas) and the development of an implantable mechanical B cell.

Pancreatic Transplantation

Studies using adult isolated islets, dispersed fetal or neonatal pancreas, or minced adult pancreatic fragments with or without prior culturing have clearly demonstrated the ability of iso- or auto-transplanted pancreatic tissue to permanently cure experimentally-induced diabetes in mice, rats, dogs, pigs, and monkeys (for review see references 19-21). Although various techniques have been used to implant tissue (e.g. intraperitoneal, splenic/portal vein, beneath the renal capsule,[18-22] the optimum approach appears to be the use of minced neonatal or adult pancreatic tissue implanted into splenic or portal veins; this method permits the cure of diabetes with the least amount of tissue (less than one pancreas) since it places B cells at a favorable location downstream from the liver and minimizes damage that can occur during separation of endocrine and exocrine tissue.[23,24] Though technically more difficult and prone to more complications, whole organ pancreatic transplants have also resulted in permanent cure of diabetes in experimental animals (for review see reference 22). Nevertheless, rejection of allografts remains a major problem with both tissue and whole organ transplants.[25]

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*Associate Professor of Medicine and Physiology; Director Diabetes and Metabolism Research Laboratory; Mayo Clinic and Mayo Medical School; Rochester, Minnesota.

The promising results in animals have encouraged attempts to transplant pancreatic tissue in man. The results of human organ transplants are summarized in Table 1. To avoid the problems associated with this procedure, current emphasis is on the use of minced pancreatic tissue or isolated islets predominantly the former. Table 2 summarizes the initial experience of the University of Minnesota, the leader in this area.[26] While no adverse effects to patients were observed, three major problems were identified: procurement of sufficient tissue, preservation of tissue, and allograft rejection. The latter appears to be the most formidable problem since cryopreservation[27,28] and organ or tissue culture[29–31] have resulted in preservation of functional B cells for periods as long as nine months and may permit banking of donor tissue. Moreover, autotransplantation of minced pancreatic tissue, which circumvents the problem of allograft rejection, has recently been reported[21] to be capable of maintaining normal glucose tolerance in a patient who had undergone pancreatectomy for chronic pancreatitis. Although various immunologic maneuvers have thus far failed to prevent allograft rejection,[25] two recently described techniques employing the implantation of islet tissue within artificial capillaries[32–34] or millipore filters[35] may circumvent this problem in man. These systems permit diffusion of small molecules such as glucose and insulin but not lymphocytes or large molecules such as antibodies. Successful allografts have recently been reported in streptozotocin-diabetic rats using minced neonatal rabbit pancreata implanted intraperitoneally within nucleopore filter chambers.[35]

Mechanical B Cell

Work is currently underway in several laboratories on the development of an implantable mechanical insulin delivery system. Such a device would contain a miniaturized power source and glucose sensor linked to a minicomputer which would regulate the release of insulin from a reservoir. Prototypes have already been used in animals on a short-term basis;[36] the main problems encountered are compatibility (certain parts become clogged) and the need for a long-lived power supply and a glucose sensor with sufficient reproducibility and specificity. A larger nonimplantable prototype called the Biostator is commercially available (Life Sciences Division, Miles Laboratories, Elkhart, Indiana) and has been used experimentally

TABLE 1

Current Status of Human Pancreas Transplantation*

Type	
Pancreas alone	
Total	1
Subtotal	22
Pancreas-Subtotal + Kidney	8
Pancreas-Duodenum	6
Pancreas-Duodenum + Kidney	20
Total	57

Results

All recipients have died or failed to retain transplant; four recipients who survived more than 10 months with functional allograft had correction of abnormalities in glucose metabolism. Longest survival was four years.

Problems

vascular thrombosis, drainage of pancreatic duct, autodigestion, graft rejection and associated complications, donors' need for immunosuppression

*American College of Surgeons-NIH organ transplant Registry December 1966-July 1977.

TABLE 2

Summary of University of Minnesota Experience with Pancreatic Tissue Transplantation in Man[26]

Recipients

Seven insulin-requiring adult diabetics (aged 23-49 yrs) on immunosuppressive regimens because of prior renal transplantation were subjected to ten transplantation procedures.

Tissue

Pancreatic tissue was obtained from brain-dead cadavers; minced tissue from six infants (2-12 mos old) and isolated islets from four adults were used. The islet transplanted ranged from 0.4% to 14% of a normal adult pancreas.

Route of Administration	
Intramuscular	1
Intraperitoneal	5
Portal vein	4
Results	
Insulin independence	0
Reduction of insulin requirement	4/4 Portal 3/5 Intraperitoneal
Average	51 ± 6%
Duration	2-9 wks, longest 18 mos
Adverse effects	No peritonitis, hepatic dysfunction or deterioration in renal function.

and therapeutically in man.[37,38] This device, (Figure 1) measures circulating glucose levels six times a minute during continuous withdrawal of blood and, by means of computer-directed infusions of insulin or glucose, can achieve and maintain virtually any desired plasma glucose level within the physiological range. It could find widespread use as an adjunct in the management of ketoacidosis and of diabetics undergoing surgery.

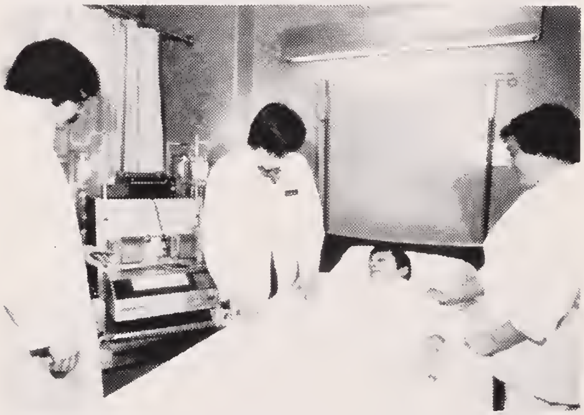

Fig. 1 — The Biostator, a mechanical artificial B cell, in operation on the Clinical Study Unit at the Mayo Clinic.

Enhancement of Insulin Action

Most patients with diabetes mellitus have maturity onset-type diabetes. Although these diabetics have normal or elevated circulating insulin levels, a degree of insulin resistance is present which exceeds the capacity of the diabetic B cell mass to increase its insulin secretion. In the obese diabetic, this insulin resistance is associated with a decrease in the number of insulin receptors.[39] Accordingly, development of agents which would increase the number of insulin receptors or their affinity for insulin might be useful in the treatment of adult onset-type diabetes. Indeed, chlorpropamide has been reported to increase the binding of insulin to circulating monocytes of patients with adult onset-type diabetes[40] and might serve as a prototype for such agents. A new orally effective hypoglycemic agent (McN-3495), structurally dissimilar to biguanides and sulfonylureas, lowers plasma glucose levels without apparently increasing insulin secretion[41] which suggests that it may act by increasing the effectiveness of insulin. Preliminary testing of this compound in man is under way.

Another approach to enhancing the action of insulin is the diminution of hormonal insulin antagonists such as growth hormone and glucagon. Preliminary studies employing somatostatin for this purpose have shown promising results.[38,42] This peptide, originally discovered by Guillemin and his associates at the Salk Institute in the hypothalamus of sheep, inhibits the secretion of numerous hormones including insulin, growth hormone, and glucagon. It has several other nonendocrine actions including inhibition of gastric and pancreatic exocrine secretion.[43] These actions and the short halflife of somatostatin (one half to two hours subcutaneously) currently limit its use to purely research situations. Nevertheless, as shown in Figure 2, intravenous infusion of somatostatin markedly enhances the effectiveness of conventional insulin therapy in insulin requiring diabetic patients. In these studies, somatostatin plus insulin was more effective than twice as much insulin alone in controlling hyperglycemia and resulted in near normalization of diurnal plasma glucose levels in the subjects studied. Because somatostatin without accompanying exogenous insulin worsens diabetes of the adult onset-type,[44] work is under way to develop longer acting and more specific analogs of somatostatin; promising results have been reported in various animal models with several compounds.[45,46] These agents are currently awaiting Food and Drug Administration approval for testing in human subjects and conceivably could be in use as an adjunct to insulin prior to the practical application of pancreatic transplants or an artificial B cell in the treatment of diabetes.

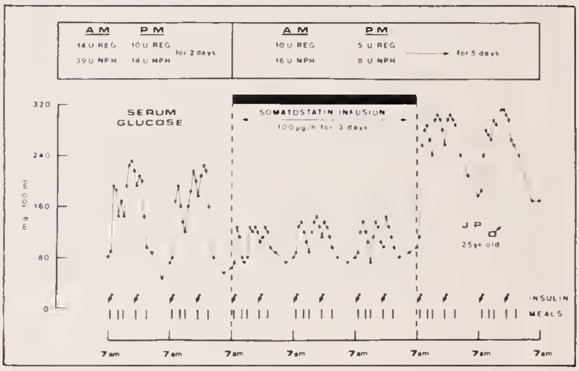

Fig. 2 — Comparison of 77 U insulin/d alone (first two days) 39 U insulin/d plus somatostatin (middle three days) and 39 U/d insulin alone (last two days) in the management of a juvenile-onset diabetic patient (for experimental details see reference 39).

Biochemical Intervention at the Cellular Level

Theoretically, once the biochemical mechanisms responsible for the development of the long-term complications of diabetes become known, it should be possible to develop the means to reverse or inhibit these processes. The currently most promising prototype for such an attack is diabetic neuropathy.[47,48] In neural tissue the transport of glucose across the extracellular membrane does not require insulin;

during episodes of hyperglycemia, intracellular free glucose may accumulate and be metabolized by pathways not normally used, i.e. via aldose reductase to sorbitol.[47] The accumulation of polyols such as sorbitol which are not readily transported out of the cell may cause osmotic damage. Associated with the accumulation of sorbitol is the depletion of nerve myoinositol.[6] In experimentally diabetic rats, meticulous control of hyperglycemia replenishes neural myoinositol concentrations and restores nerve conduction velocities to normal; however, dietary supplementation of myoinositol without correction of hyperglycemia has a similar effect.[6] Thus, in human diabetes myoinositol supplementation might lead to improvement of diabetic neuropathy. Similarly, the use of agents such as aldose reductase inhibitors may prevent the accumulation of polyols and may also have beneficial effects.

Another potential area for biochemical intervention is the abnormal platelet function reported to occur in diabetics.[49–51] Increased sensitivity to aggregation and increased production of prostaglandin E-like material in response to epinephrine and collagen are known to occur.[52] Since platelets, during their interaction with blood vessel walls, release factors which stimulate smooth muscle proliferation and enhance endothelial permeability, abnormal platelet function could be important in the pathogenesis of some of the long-term complications of diabetes. Although meticulous control of hyperglycemia has been reported to improve platelet function in human diabetes,[53] considering the current methods available to treat hyperglycemia, the use of agents such as aspirin[54] or propranolol[55] to diminish platelet sensitivity to aggregation may prove more practical.

Adjuncts to the Assessment of Diabetic Control

As stated earlier, hyperglycemia is but one of the chemical abnormalities found in diabetes, and the relative importance of hyperglycemia per se in the production of the long-term clinical manifestations of insulin deficiency is still unclear. As more becomes known of the other chemical abnormalities, determinations of Von Willebrandt's Factor,[49,50] platelet function,[49–53] beta thromboglobulin,[54] or urinary myoinositol[55] may prove more pertinent to the evaluation of the efficacy of therapy against the long-term complications of diabetes. For the present, however, glucose appears to be the best modality available. Unfortunately, determinations of glycosuria are not particularly reliable and are too insensitive to monitor the degree of metabolic control apparently required to forestall the complications of diabetes; determinations of plasma glucose levels on a given day are subject to considerable bias (desire of patient to appear in good control-low level, stress-high level) and thus may not necessarily reflect the usual degree of diabetic control.

The recent discovery that hemoglobin becomes irreversibly glycosylated during periods of hyperglycemia resulting in increased levels of hemoglobin A-1C (HbA1C) may provide a means of assessing the adequacy of diabetic control over a prolonged period of time.[56] HbA1C results from the spontaneous covalent addition of a glucose molecule to the N-terminal valine of the B chain of hemoglobin and normally is only a small fraction of the total hemoglobin present in red blood cells (2-5%).[57] The amount of HbA1C can be increased *in vitro* by incubating red blood cells in high concentrations of glucose[58] and can be increased *in vivo* during hyperglycemia as has been observed in animals after experimental induction of diabetes.[59] Once formed, HbA1C persists for the lifetime of the red blood cell. Thus the amount of increase in HbA1C present at a given time reflects the degree of antecedent hyperglycemia.

Patients with either adult onset or juvenile onset diabetes who are in poor control have elevated levels of HbA1C[60–65] which can be lowered to normal after six to eight weeks of meticulous control of hyperglycemia.[53,62] In general, there has been a good correlation between antecedent hyperglycemia or glucosuria and HbA1C levels.[62–65] Thus a single HbA1C determination, which reflects time-averaged plasma glucose levels, may be used as an index of diabetic control and the adequacy of treatment during periods between clinic visits. At the present time, however, HbA1C determinations are not widely available on a routine basis but could readily become so should further evaluation support their usefulness. Parenthetically, HbA1C binds oxygen more avidly than hemoglobin A and releases less oxygen than hemoglobin A at the tissue level; since hemoglobin A1C levels over 15% have been reported in diabetic patients,[63] local anoxia due to this may be a contributory factor in diabetic microangiopathy.

Summary

As recent evidence supports the conclusion that the long-term complications of diabetes may be prevented or ameliorated with improved metabolic control, current research has centered around several innovative approaches to achieve better control: (1) A more physiological means of insulin delivery than daily or twice daily insulin injections, e.g. pancreatic transplantation or mechanical beta cell. (2) Agents which either enhance the effectiveness of insulin through alteration in hormone — receptor interaction (e.g. chlorpropamide) or reduce the hormonal antagonism to the action of insulin (e.g. somatostatin). (3) Agents which may directly interfere with the development of abnormal nerve conduction (e.g. myoinositol) or platelet adhesiveness (e.g. aspirin). (4) Additional parameters to accurately assess the degree of metabolic control exclusive of random blood and urine sugars, e.g. hemoglobin A-1C.

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15-65. May be secured from the author.

Cover Photograph

"Human Islet of Langerhans"

The cover shows a photomicrograph of an islet of Langerhans isolated from a human pancreas. The original magnification is X 400. The islet is stained with aldehyde fuchsin and shows beta cells containing purple insulin granules.

Dr. David Sutherland, who donated the picture, is a surgeon at the University of Minnesota. The islet was isolated during experiments performed in collaboration with Drs. Michael W. Steffes and John S. Najarian. Islets are liberated from the rest of the pancreas by collagenase digestion of minced pancreatic fragments. The islets are separated from the non-endocrine pancreatic tissue by centrifugation in a discontinuous density gradient of Ficoll (a polymer of sucrose). Islets are lighter than pancreatic acinar tissue, and localize at the upper portion of the gradient. The islets are viable as demonstrated by their ability to secrete insulin in response to glucose stimulation.

Notice of Special Studies

Studies of associations between diabetes and HLA antigens are being conducted at the University of Minnesota Medical School. The results of these studies depend on tissue typing a large number of diabetic patients of all types. I would like to invite all interested physicians to contact me for this purpose. This service would be provided free of charge, would require only a small blood sample, and the results would be made available to the physician. It is likely that the HLA antigens will have clinical applications in the future (see article on the genetics of diabetes)*.

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See page 14

Special Article

Living with Diabetic Children

A Family Affair

GEORGE MAGNUS JOHNSON, M.D.* and JANICE B. JOHNSON, B.A., M.S.†

A sound educational effort, a chance for the diabetic child to define his own normality, an understanding of individual family values, and discipline are four elements necessary to successful living with juvenile diabetes. However, problems arise.

MY WIFE REMEMBERS that day more than ten years ago:

> Our oldest son had the "flu" over Christmas. Then I got it. I spent Christmas Day clad in my robe sitting in the kitchen rocker with the baby, Christian. I was recovering but Nels was still vomiting after three days. At mid-afternoon on one of our frequent visits to his upstairs bedroom we discovered that his breathing was shallow but hollow sounding and strangely sweet. Even though it was Christmas Day, he had no inclination to come downstairs. At a little after five George came into the kitchen carrying our seven-year-old son wrapped in blankets.
>
> "Help me get his parka on him," George said tensely. Nels was unconscious.
>
> At that moment the word "diabetes" jabbed our consciousness. The shock of the discovery was compounded by the irony of our situation: Nels' father is a pediatrician.

My being a pediatrician notwithstanding, our experience has been repeated in many families and while it is always stunning, it is not remarkable. Unless we are already closely acquainted with a person who has diabetes, we probably seldom think of the disease, and when we do, we think more often of middleaged, overweight people than children. So it is safe to say that most of us whose children become diabetic begin with quite the same period of shock. It is in the first weeks and months after the numbness has worn off that we reassemble our values, gather our resources, and come to terms with the new reality: we are a diabetic family.

As parents, our first instinct was to educate ourselves. Even though I was a board certified pediatrician with three and a half years in practice, I had had virtually no contact with juvenile diabetes. My only exposure had been academic. The same was true of our son's physician. Thus, we had to initiate our own education, and though we were highly motivated we got off to a dismal start by pulling off the shelf every book which had some reference to juvenile diabetes. One of the first was an authoritarian tract which defined the disease absolutely, outlined management by proscription, and stated the prognosis as "X" years from onset to demise. That was ten years ago. Fortunately, today that dismaying initiation need not happen. Most physicians are familiar with either a nearby hospital-based diabetes course or with a comprehensive education center such as in Minneapolis or Duluth. A thorough educational program involving the patient and the family as participants "not as patients" during the early stages of the disease is essential, in my opinion. It lays the groundwork for a healthy emotional outlook and helps make the demands of diabetes management acceptable. It also emphasizes the importance of family responsibilities.

Most desirable is an educational effort by the family physician or pediatrician, using other local resource people such as dietitian and nurse-educator in an established routine for all newly diagnosed patients. But not all clinicians have the interest, knowledge, or time to devote to this demanding and time-consuming regimen. The alternative is the full-fledged diabetes education center. To repeat: A thorough patient-participant educational program as close to onset as reasonably possible is the best assurance of a stable emotional milieu in which to begin to manage juvenile diabetes. This is my conviction from my observations as a clinician, based upon my personal perspective.

In addition to education there are, it seems to me, a few other considerations. Diabetes unlike many other more acute diseases presents conflicting definitions. On the one hand it is a disease which must be treated properly; on the other it is simply a way of life not to be thought of as remarkable or limiting. It's easy to "live" with the "24-hour flu." You stay in bed until the symptoms recede. But how do you live with something that never goes away, does not distinguish you in any apparent manner from your fellows, needs proper amounts of good food and insulin, plenty of regular strenuous exercise, and requires constant vigil? Obviously, either you become neurotic or you develop the methods and perspectives to allow a "normal" life.

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*Pediatrician at the Fargo (North Dakota) Clinic. He is President of the North Dakota Diabetes Association and Co-Director of Camp Sioux.

†Master's Degree in community and regional planning and teaches English at North Dakota State University.

Normal. What is that? It's a child eating cotton candy at the state fair. It's a 12-year-old at a slumber party. It's a young man drinking a boastful beer at 16. It's ice cream and cake at a birthday party. It's not diabetic. Don't ever tell a kid who has diabetes that he's "normal-except for your diabetes." *He* knows what normal is. Let him fit himself into the picture. Don't lie. Don't commit fraud. Forgive me these negative strictures, but they are simply the reverse of what is so often handed out to our young patients. If we physicians, nurses, and dietitians can do something to correct the negativism and outright dishonesty which have all too often ruined relationships with adolescents who have diabetes, we will have achieved much. It's hard for doctors, and certainly for parents, not to be prescriptive, proscriptive, and bossy. Likewise, it's sometimes hard for the young people to accept the "wisdom" we so badly need to impart.

Given that today's new diabetic families will have sound preparation for living successfully with diabetes, they still must reaffirm and perhaps reorder their values. My wife and I did this in the first days. Number one on our list of important values for our diabetic sons (our youngest child became diabetic less than a year after his brother) and their non-diabetic brother was independence. Above all, we felt we must give them the strength, background, and tools for independent life. From the beginning we agreed that we would not make up excuses, nor allow them, based on diabetes. We would encourage self-care in stages appropriate to age and development without browbeating. (Our children were nine or ten before they gave their own injections. Others may accept that chore sooner without undue forcing.) And, most important, we would try our hardest to give our boys a wealth of experience before they had to meet life on their own. By definition that means hard, unpleasant times as well as joyous, warm ones. It means being trained to eat correctly and to prepare a meal. It means being able to take care of the household for a week without mother. It means being driven, sodden and sleepless, from a canoe trip by a nine hour deluge. It means camping in a rattletrap VW bus for two weeks in Iceland. It means having a special and private place where we as a family go by ourselves to be free of intrusion and everyday distraction. It means hiking deep into the wilderness beyond the reach of modern conveniences for a breath of pure air, a feeling of the essential. We cannot live our children's lives for them. We can only give them, to the best of our various abilities, the strength and the tools to live life with confidence.

Not everyone would choose or is able to use our specific methods. That is not important. But it is important that each parent-couple agree openly, verbally, on the goals they wish to establish for their children. The context here is diabetic, but it really should not be so. All parents should consciously undertake this exercise in the hope of greater family solidarity and understanding.

There is a fourth element necessary to successfully live with juvenile diabetes, as I see it. It is discipline. In contemporary psychological circles this is not a fashionable word. In the context of diabetes mellitus it is crucial. For the young diabetic discipline means eating the right foods at the right times. Discipline is shunning many of the snacks and treats his friends dote on and choosing acceptable substitutes. Discipline is testing and recording regularly and accurately and interpreting these records correctly — while visiting friends, on camping trips, on Christmas Day. Discipline is exercising after meals — during rainstorms and blizzards, when tired or with company. Discipline is a way of life. It goes a long way toward helping the young diabetic to define "normal."

These are not magic words. Dealing with a young person honestly, guaranteeing his independence, and establishing pride in a sense of discipline will surely help to create emotional stability for a diabetic family. But they cannot substitute for a thorough educational program early in the course of the disease. On the other hand, if a couple enjoys a secure and happy marriage, the chances for a stable emotional atmosphere in their family are great — diabetes or no.

So much for goals and ideals. We are not able to achieve all we set out to — no one can. In our family we have had two especially vexing frustrations: getting the boys to test four times a day (they balk at more than three) and maintaining a consistent level of exercise after supper. For some reason we have not succeeded in impressing our sons with the importance of urine test recording. Some fault is no doubt due to our own rather compulsive personalities which tend to equate "0" with perfection and 4+ with sloth. We know, rationally, that this is an improper approach, and we try to mitigate it — still . . . There is some indication that our oldest son's recent solo visit to an education center may have improved his habits. My wife finally hit upon a quiet method of reminder after several unrecorded urine tests slip by unnoted. She takes the offender's test booklet and writes his name in large letters across the "comments" side of the page, then props it up over the testing materials so he can't miss it. This technique seems to engender less resentment than vocal ones.

Exercise can be a great annoyance, especially with younger children. For even though it seems that youngsters are on the move every minute, that may be more appearance than fact. It's hard to get a 7-11 year old to be consistent about after-meals exercise. The parent (I, my wife) nags; the child whines, drags his feet, pleads fatigue, and then slinks away in contradiction to your orders. First, the parent gets mad; then he sinks into a chair and says self-pityingly, "What am I going to do — I try so hard." It's an exasperating scene and we've never found a happy, foolproof solution. Sometimes the desire for full bedtime snack is adequate incentive to run off a 3 or 4+. But not always. It is handy to remember that most houses come equipped with fine exercise apparatus — a staircase. Running up and down a flight of stairs a number of times is not very exciting but it does the job. Our oldest son has adopted running. He runs several miles three or four nights a week, usually after supper. He also does hard physical work frequently. The test will be when he is away at college — will he maintain his routine?

Implicit in both these kinds of problems is the setting for bickering. Regrettably, we have been more than guilty of that devisive and insidious activity. In the drive for good control — a necessary and worthy pursuit — it is all too easy to be distracted by unimportant details such as how often tests are checked by a parent for accuracy (sensitive diplomacy required) or how many doughnuts somebody has eaten today. Once the conversation has veered off into this hostile territory, the goal itself is obscured. The trick is to tune your ear so that when you hear it start, you can check yourself.

Some problems, on the other hand, are almost impossible to correct regardless of effort. An example is controlling fats-lipids in the diet. Nutritionists, cardiovascular specialists, and other experts exhort us to curtail intake of saturated fats and to reduce the percentage of fat in the total diet. So what do you eat for breakfast, or more to the point, what do you get a child to eat for breakfast? We've been taught that the distribution of nutrients should be fairly evenly divided throughout the day. But protein choices for the morning meal are overwhelmingly high in saturated fat and/or cholesterol. Try offering a 10-year-old low-fat cottage cheese and fish for breakfast. We have. Once. There are acceptable foods — thinly sliced breakfast steaks and Canadian bacon, for example — but they are very expensive and tiresome if presented ad infinitum. The only solution seems to be to increase servings of skim milk some mornings and add a little peanut butter or a small piece of cheese and skip the meat and eggs. Unfortunately, having taken care of fatty breakfasts, we arrive at lunch. This meal is the bane of my wife's meal planning. Everyone hates it. During the school year we pay the boys the price of school hot lunch if they will take their own bag lunch from home. Even when the pay is prompt, this is not a happy arrangement. It is not so much that they would rather eat soggy french fries, greasy sandwiches, cremated corn, or dry hamburgers. They just don't like lunch. Nevertheless, they do reluctantly make and take their lunch at least three times a week. The high school student occasionally eats school fare because there is some range of choice. The grade school student, however, must come home if he doesn't pack his lunch because the cafeteria menus are laden with fats and concentrated carbohydrates and there is no alternative selection. Of course, carrying homemade lunch doesn't guarantee good nutrition. Processed meats and cheeses are extremely high in fat and items such as lean ham, roast beef, and sliced chicken are too expensive to use frequently. One type of sandwich filling our boys will eat without much grumbling is either salmon or tuna salad which my wife makes with a combination of low-calorie salad dressing and mayonnaise or oil and vinegar dressing and adds a healthy portion of chopped celery and onion for crunch and flavor. Our oldest son rejects fruit with the exception of a few seasonal exotics so we have to sneak oranges into his lunch bag when he isn't looking. What they are traded for we will never know. We often use cookies for dessert, nearly always homemade. Janice uses a formula of ½ c. sugar to 2 cups flour (plus margarine, egg, and other "additives") to make four dozen cookies — or two per bread exchange or two per calorie point. Our youngest son is an avid baker and he has adjusted his favorite recipes ("chocolate shadows," "chocolate-covered fingers") to meet the formula. We limit the amount of this kind of treat to one serving per meal. It does not appear to distort test results.

But some eating does. And it is inescapable. A grade school child is a highly social creature. His friends and peer activities are terribly important to him. They are far more important, in my mind, than good tests *all the time*. The caution is that this relaxation of usual routine not become habit itself or be taken for granted. We have never called our son's hostesses before a birthday party or an overnight, feeling that would somehow violate our trust in him. We have instead, rightly or wrongly, placed the responsibility on him by instructing him in how to make choices. Admittedly 4+s have often resulted. But it seems the child's integrity remains intact.

Most of us parents seek the warm glow of satisfaction, knowing that we have expected a reasonable level of responsibility from our children, knowing that we have made them do some things for their own good. Sometimes, though, we are left in consternation, perplexed by an unexpectedly tenacious refusal. Such was our experience when we announced to our 17-year-old son that he should plan to attend a diabetes education center for a week on his own. It required the sacrifice of a week's pay which would have come from his part-time job. It also thrust him into a situation in which he had to *think* about diabetes. These were large demands, perhaps too large. The resistance lasted throughout the course and the final evaluation was that the course had been "a waste of time." He acknowledged that he learned "a few" things — principally the substitution of a calorie point system for the exchange method of diet planning. For us, his parents, this was a troublesome decision. Perhaps in our zeal we demanded too much. When will we know whether his negative reaction was only a temporary response to an unwanted experience or a permanent resentment to an injurious betrayal of trust? We *think* we did the right thing by forcing him to face up to some of the unpleasant realities of diabetes so that he can deal intelligently with them. We *think* we did right by insisting that he take advantage of this opportunity to ask the questions that must be on his nearly-adult mind of people who are interested, yet disinterested. We *think* we did right, but we don't know.

It may be that our son was conditioned by us to his harsh rejection of the diabetes center. For in all cases of chronic disease or disability some degree of denial must be present to balance the concern, the worry, the apprehension. In the case of diabetic children it is a difficult matter, and perhaps we in our family have gone too far in denying the disease. In our effort to help our sons define their own normality we may have allowed ourselves and our sons too many moments free of constraint. That there must be some denial to act as a leveling mechanism for the personality is apparent. How much, how often is not so clear. We have, as it were, escaped to our cabin, to the wilderness, to foreign lands, to books — retreats which give us the illusion of freedom, some space to breathe unfettered. But these are only illusions and even within them the strictures are there. Have we told our boys that there are places to go, either in mind or in person, where the demands of their condition do not manifest themselves? If we have, that was not our intent. We wanted only to show them these life-saving outlets and how to take advantage of them. We know there is no real denial. We are a diabetic family. We will always be one. Can we not be an adventuresome one, sometimes?

Continuing Medical Education

New Mexico Metabolism Symposium
March 8, 9 & 10 1979 — Taos, New Mexico

Fourth annual meeting on Diabetes and Related Disorders. In addition to in-depth discussion on changing concepts in the field of diabetes, the program will provide opportunity to take advantage of New Mexico's fine powder skiing. Further information: Office of Education, Lovelace Medical Center, Albuquerque, New Mexico. (505) 842-7353.

American Diabetes Association

THE AMERICAN DIABETES Association, Minnesota Affiliate, Inc. (ADAM), has been in existence just four years. In that brief period, tremendous growth has occurred. A committed staff of four persons and hundreds of energetic volunteers have brought ADAM to the point where today we have three chapters and over thirty units. ADAM's gross revenue, which included the national Holiday Card Program, went over one million dollars for the first time in 1977.

Extensive programming is carried out in professional education, patient education, public information and research. ADAM's professional education committee is an active group of professionals constantly seeking out and recommending new approaches to professional education. Three regional diabetes symposia are held annually to help physicians stay current with new developments. Serious thought is being given to supplementing the symposia with one day workshops which would be presented on a regional basis. ADAM has an extensive library of brochures, booklets, and pamphlets for use primarily by diabetics and their families but are available to any physician requesting them. ADAM continues to produce the one-half hour television series "The Diabetic Today" directed to diabetics and their families. In 1977 nearly $420,000 raised by ADAM went to fund research grants and awards at the state and national level.

During 1977 and 1978, the Diabetes Education Around Minnesota (TEAM) Project has been in action. This is a cooperative educational effort between ADAM and the Diabetes Education Center with funding through the McKnight Foundation. To date, over 45 day-and a half workshops have been co-sponsored with at least 43 communities. This project has been extremely successful. Over 370 physicians have attended the scientific sessions with over 4,400 people attending the educational program. Approximately 30 health professionals have attended the week long Diabetes Education Center classes as part of the TEAM program and now serve as resources in their communities. ADAM intends to continue the TEAM Project with some modifications including follow-up with the health professionals serving as resources. Physicians should be aware of such resource people available in their or nearby communities so they can communicate the access of such resources to the diabetic.

Being a diabetic, I am keenly aware of the intensive education that is required for the diabetic so he/she can make appropriate day-to-day changes in diet, exercise, insulin dosage, etc. Advice from the physician, based on regularly scheduled visits, is essential to effective treatment and control; however, additional education must occur over and above what can be accomplished in an office visit. The physician can play a significant role at that point by informing the patient of materials, educational classes, television programs, people resources, organizations, etc. which are available to help educate the patient.

For a nominal membership fee ($12) a person can become a member of ADAM which includes membership in the local unit and the American Diabetes Association. It entitles the registrant to the ADA Forecast magazine (bi-monthly) and the monthly newsletter ADAM in ACTION. ADAM's chapters and units hold regular monthly educational meetings. Diabetics should be encouraged to become members of and be active in their local unit or chapter.

Successful management and control of diabetes involves what I call a team approach. It involves cooperation and concern. The team includes the diabetic, physicians, nurses, dietitians, other health professionals, family members, and others. Each contributes in his/her own way to assist the diabetic with control. However, especially in newly diagnosed diabetics, if the physician does not take the initiative to inform the patient of resources available, the team may never effectively be formed.

ADAM is at the forefront of organizations leading the fight against diabetes. We are on the cutting edge of formulating new and innovative programming and fund-raising. ADAM needs all the help it can get-both money and volunteers. Physicians and health professionals play a big role in ADAM and many are active and supportive over and above their professional capacity. We have included the names and addresses of our chapters and units.* Please contact any one of them and do your part in our fight against diabetes and its complications. We also include a coupon which can be clipped and sent to ADAM if you desire membership, information on materials available, shipment of specific materials, or any other information about ADAM. † We ask your commitment to our cause.

David L. Zuelke, President
American Diabetes Association,
Minnesota Affiliate, Inc.

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*See page 65.
†See page 66.

Index to Advertisers

American Medical Association 37

Anderson, C. F. Co 30

Beltone Electronics Corporation 12

Burroughs-Wellcome Co. 58

Classified Advertising 67

Lilly, Eli & Co. 4

Medical Protective Company 6

Mediclinics 24

Merrell-National, Inc. 17,28,29,30,56,57

Minnesota Medical Association 2

New Mexico Metabolism Symposium 54

Pfizer Laboratories 8

Prevention of Blindness 40

Roche Laboratories .... Cover 2,18, Covers 3,4

Smith, Kline & French 27

United States Air Force 6

Upjohn Company 38,39

Tenuate® ⓒⅣ
(diethylpropion hydrochloride NF)

Tenuate Dospan®
(diethylpropion hydrochloride NF) controlled-release

AVAILABLE ONLY ON PRESCRIPTION
Brief Summary
INDICATION: Tenuate and Tenuate Dospan are indicated in the management of exogenous obesity as a short-term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors inherent in their use such as those described below.
CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).
WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence.* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.
OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

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Direct Medical Inquiries to
MERRELL-NATIONAL LABORATORIES
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References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

Merrell

8-3921 (Y587A)

Whether overweight is a complicating factor... or just uncomplicated overweight.

Tenuate® Dospan® ⓒⅣ
(diethylpropion hydrochloride NF)
75 mg. controlled-release tablets

A useful short-term adjunct in an indicated weight loss program.

Overweight patients in certain diagnostic categories often require strict obesity control. Diethylpropion hydrochloride has been reported useful in obese patients with hypertension, symptomatic cardiovascular disease, or diabetes. While it is not suggested that Tenuate in any way reduces these complications in the overweight, it may have a useful place as a short-term adjunct in a prescribed dietary regimen. (Tenuate should not be administered to patients with severe hypertension; see additional Warnings and Precautions on the opposite page.)

In uncomplicated obesity.

Many patients, on the other hand, present with excess fat but no disease. While this condition is often termed uncomplicated obesity, complications of both a social and a psychologic nature may be distressingly real for the patients. In these cases, a short-term regimen of Tenuate can help reinforce your dietary counsel during the important early weeks of an indicated weight loss program.

Clinical effectiveness.

The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

Tenuate—it makes sense. And it's responsible medicine.

Merrell

For prescribing information see opposite page.

EMPIRIN® COMPOUND
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Each tablet contains aspirin, 227 mg, phenacetin, 162 mg, and caffeine, 32 mg; plus codeine phosphate in one of the following strengths #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛). (Warning—may be habit forming). CIII

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Minnesota Medical Association

Syllabus

A compendium or summary outline of a discourse, treatise, course of study or examination requirements; a series of abstracts. (Webster)

This issue of *Minnesota Medicine* starts a new and innovative educational project, the CME SYLLABUS of the Minnesota Medical Association Scientific Assembly. Each syllabus summarizes a presentation given at the outstanding annual MMA meeting in Duluth in May, 1978, where many registrants were able to renew or expand their knowledge at well-planned workshop seminars devoted to selected medical subjects.

A syllabus (as Webster notes) cannot substitute for the electricity developed or the depths plumbed when smart people interact in a learning situation. It is not meant as a substitute for a detailed and edited formal paper. A syllabus, when supplied to participants at a meeting, does assist the orderly presentation, transfer, and accumulation of information. Thereafter, it serves as an outline to assist, recall, and organize further self study.

Admittedly, when a syllabus is presented without the reader's having experienced the live seminar, some potential is lost. However, the opportunity to have available a thoughtful, scholarly, and organized broad outline of a subject should save some of us many moments of searching before we settle comfortably into our study chairs.

A different syllabus will be published monthly in *Minnesota Medicine* and should become a part of your reading file. As you study these published pages (prepared by the discussion leaders and published by the urging of Stuart Thorson, MMA Scientific Assembly Subcommittee Chairman), you should also remember to start making notes on your calendar to attend the MMA meeting *next* May in St. Paul.

And, let us know if you find the CME SYLLABUS-MMA as useful to you as a reader as the 1978 program participants already have indicated!

J. S. Welch, M.D.
Rochester, Minnesota

Dizziness

The symptom complex of dizziness is one that confronts most physicians almost daily in the care of their patients. Dizziness knows no age limits or sex bias, and quite often requires the input of many physicians before a specific diagnosis is made and therapy instituted. Unfortunately, many cases of dizziness are labeled as "labyrinthitis" or "Meniere's disease" without substantiation, deferring the actual diagnosis and perhaps specific therapy. Even though all physicians see patients with this symptom at one time or another, the three specialties who seem to be primarily consulted regarding this troublesome problem are otolaryngology, neurology and internal medicine or cardiology.

Melvin E. Sigel, M.D.*
Moderator

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*Clinical Professor, Department of Otolaryngology, University of Minnesota, Minneapolis.

Vertigo

A. B. Baker, M.D., Ph.D.[*]

Dizziness is one of the most common neurologic complaints. When a physician encounters this complaint he must first determine whether the patient has a true vertigo or not. A *true vertigo* refers to a sense of movement either of the subject or the environment. The more common complaint of dizziness refers to a sense of "giddiness" or "light-headedness" in which no movement sensation occurs. Vertigo usually indicates a lesion below the tentorium. Vertigo can be caused by a lesion of the vestibular system. This may be peripheral (semicircular canals, vestibular nerve) or central (vestibular nuclei, tracts in the brainstem, cerebellum or cerebrum). The characteristics of vertigo vary, depending upon whether it is central or peripheral.

There are many causes of vertigo. Only the more common ones will be considered according to their occurrence in the different age groups.

Infancy and Childhood

1. *Infections* — (Encephalitis): Usually nonspecific infections; may occur with the purulent meningitides or mumps; acute onset; self-limited course with recovery in a few weeks; peripheral type of vertigo; treatment symptomatic.

2. *Cerebellar tumors:* Astrocytoma or ependymoma; associated with incoordination and signs of increased pressure (headache, papilledema).

3. *Pontine tumors:* Pontine glioma; gradual onset; associated with other cranial nerve involvement; progressive course even though vertigo may improve temporarily.

Adult Vertigo

1. *Meniere's Syndrome:* Labyrinthian disease (hydrops); acute onset; marked accentuation by head movement; marked nausea; paroxysmal; tinnitus and deafness; no central nervous system involvement; spinal fluid normal; self limited course but recurrent. TREATMENT: With vasodilators (niacine, Benedryl; Histamine; I.V. Procaine).

2. *Multiple Sclerosis:* Most common neurological cause of vertigo; remissions and exacerbations; other neurologic complaints and disabilities; scattered neurologic findings; progressive course.

3. *Acoustic neuroma:* Acute vertigo, slow progressive tinnitus and deafness; decreased ipsilateral corneal reflex; impaired caloric tests on involved side; increased spinal fluid protein; x-ray changes of interior auditory meatus; cerebellar findings.

4. *Trauma:* Postural vertigo accentuated by stooping or activity; associated with headache; associated memory impairment; often self limited but may persist for years. TREATMENT: Niacin; Papaverine HcL.; Potassium Iodide.

5. *Thrombosis post-inferior cerebellar artery:* Sudden onset; paresthesias and hypesthesia ipsilateral face; hypesthesia contra-lateral side of body; ipsilateral Horner's syndrome; ipsilateral incoordination; vertigo transient but may be severe for weeks. TREATMENT: Anticoagulants and bed rest.

6. *Drugs:* Salicylates, Quinine, Darvon, Barbiturates, chiefly involved; marked horizontal nystagmus; no associated central nervous system involvement; very transient — days.

Middle and Older Age Vertigo

1. *Basilar artery ischemia:* Intermittent vertigo (hrs.); intermittent ocular disturbances (diplopia); intermittent dysphagia or dysarthria; intermittent motor or sensory disturbances shifting from one side of body to other. TREATMENT: Anticoagulant therapy indefinitely.

2. *Brain Stem Hemorrhage:* Acute onset; occurs in hypertension; often an isolated finding; slow improvement (weeks).

3. *Brain Stem Glioma:* Slow onset; progressive; associated cranial nerve and long tract findings; no signs of systemic involvement.

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[*] Emeritus Regents Professor of Neurology, University of Minnesota, Minneapolis.

Vertigo as a Hallucination or Illusion

Hyman M. Paisner, M.D.[†]

Vertigo is defined as a hallucination or illusion of movement of self or surroundings.

Patients with vertigo can be divided into two catagories: (1) Those of central origin due to diseases affecting the central nervous system and (2) Those of peripheral origin due to diseases involving the external, middle and inner ear and the first order neuron (extending from the hair cell peripherally to the point of synapse with the vestibular nuclei medially).

[†] Clinical Associate Professor, Department of Otolaryngology, University of Minnesota, Minneapolis.

Central origin problems include:

1. Anxiety vertigo
2. Multiple sclerosis
3. Epilepsy
4. Ischemia due to vascular insufficiency syndromes (basilar vertebral disease, subclavian steal, Walenberg's syndrome)
5. Head trauma
6. Cerebellar or cerebral tumors

Peripheral causes include:

1. Benign positional vertigo
2. Meniere's disease
3. Acute and chronic middle ear infection
4. Mastoid disease (infections, tumors)
5. Labyrinthine infections (eg. viral, syphilis, tuberculosis)
6. Vestibular neuronitis
7. Acoustic neurinoma
8. Eustachian tube dysfunction (rare cause)
9. Cerumen (rare cause)
10. Rupture of round window membrane
11. Toxic labyrinthitis (streptomycin, gentamycin)

Questions to ask:

1. Describe vertigo in your own terms. Descriptions of vertigo due to organic disease are usually given easily. "I spin around and have to hold onto the bed." "The whole world goes round and round and I want to throw up." The patient may describe gait disturbances such as "I stumble" or "I fall against the wall." "I can't move" or "I must lie perfectly still or the spinning begins all over again."

Psychogenic disorders are described in terms that are hard to pinpoint, such as "My head feels like it's bursting", "I get funny pins and needles in my neck and face and feel faint and must lie down", etc.

2. Ask where the vertigo occurs, at what time it happens, etc. In psychogenic vertigo, they will say such things as "It always happens when I am in church or at the supermarket". In other words, it often happens in crowded areas. In organic vertigo, it can happen at any time, and when the inner ear is involved, usually is affected by movement. Patients with psychogenic disturbances often describe a feeling of unstable gait, yet a companion or observer is never aware of it. Having the patient hyperventilate often reproduces the peculiar symptoms. You should hyperventilate with the patient. They will succumb very easily — long before you do.

3. Ask how long the attack lasts.

   A. A sensation that is here and gone almost instantly is certainly most likely psychogenic.
   B. A drop attack from either basilar vertebral disease or from syncope lasts but a few seconds.
   C. Positional vertigo usually lasts longer than 15 seconds but not much longer than a minute.
   D. Episodic vertigo of Meniere's disease can last from several minutes to a day or more. But beware of your diagnosis of Meniere's disease if the actual vertigo lasts longer than a day. Lightheadedness in Meniere's disease may persist for sometime, but the actual substantial true vertigo usually has subsided within 24 hours.
   E. Vestibular neuronitis and destructive labyrinthitis (trauma, infections, toxins) can cause vertigo that can last from five days to five weeks or more.

4. Ask if there is a loss of consciousness. This almost never occurs with peripheral disorders.

5. Ask about tinnitus, hearing loss, or ear infections, or a foul-smelling ear discharge. Positive answers here will certainly direct your attention to inner and middle ear and mastoid disorders.

6. Ask about the D's.

   1. Dysarthria
   2. Disorientation to time and place
   3. Dysphagia
   4. Dysphonia
   5. Transient diplopia
   6. Drop attacks

Also ask about transient motor weakness or sensory changes. Positive answers in the elderly make you think of an ischemic process and in the young, possible multiple sclerosis. Further questioning may help reveal the localization or etiology of our problem.

A. Vascular — is there a history of migraine, coronary insufficiency, hypertension or diabetes?

B. Cancer — eg. metastasis from lung, breast or prostate, or thyroid.

C. Drugs — Use of Streptomycin, Vancomycin, Kanamycin, Gentamycin, anticoagulants that can lead to labyrinthine hemorrhage, overuse of alcohol, barbiturates, tranquilizers or hallucenogenic drugs, and the list grows and grows. More recently, Lasix has been implicated as a cause of vertigo.

D. Head injury — These are always problems in medical-legal cases. Certainly, neck injury can cause dizziness. I have too often seen nystagmus following a whiplash injury, but the mechanism is not clearly understood at present, and there are many explanations.

E. History of URI — Vestibular neuronitis often occurs in pocket epidemics following URI by about two weeks.

F. History of measles or mumps recently — These viruses can destroy a labyrinth. Indeed, mumps is one of the common causes of unilateral nerve hearing loss in children.

G. Allergic history — Ingestant allergies have precipitated attacks of episodic vertigo not unlike Meniere's disease.

H. Hypothyroidism — Seen occasionally as a cause of Meniere's disease. Replacement therapy produces a complete remission.

Physical examination includes a thorough ENT exam. Also do:

1. A fistula test — If an attic perforation exists, air pressure against the eardrum, either using a politzer bag or pneumatoscope, will cause marked vertigo and nystagmus if cholesteatoma has eroded into the labyrinth.

2. Cranial nerve examination as well as simple cerebellar tests. (Loss of coordination in the Tandem gait test may indicate cerebellar disease. Patients with psychogenic gait disorders often sidestep and hop on one foot during this test, clearly exhibiting a very healthy balance mechanism).
3. Check for nystagmus — Spontaneous nystagmus is always pathological, but in testing for nystagmus, don't move your finger beyond 30 degrees to the side, for end point nystagmus on extreme lateral gaze is found in many normal individuals. A good rule is to tell your patient to keep his head immobile, and with your finger about 18 inches away, move it laterally until you see the punctum of the lacrimal sac and the edge of the cornea in a vertical line. Nystagmus in a vertical axis is always indicative of central nervous system disease. Direction changing nystagmus is more often central than peripheral.
4. Check for positional nystagmus, and this should be routine. Unexpected positional nystagmus occurring *without vertigo* is a major sign of central nervous system disease. Check for latent period or fatigability. (Latent period meaning that there is a delay in the onset of the vertigo once the head is placed in a new position. Fatigability meaning that if the test position is repeated, the reaction becomes lessened or subsides completely.) Both these signs are indicative of peripheral disease rather than central disease.

   Audiometric tests are then done by our audiologist, and they can be very complicated. An adequate air and bone test can be done with tuning forks and a simple audiometer by any interested physician, and these tests tell you: (1) If you are dealing with a hearing loss (2) Is it symmetrical (3) Is it a conductive or sensorineural loss. Any unilateral sensorineural hearing loss must lead one to suspect and rule out an acoustic neuroma. Specialized hearing tests done by the otologist determine whether he is dealing with a cochlear hearing loss, eg. Meniere's disease, or a neural one, eg. acoustic neuroma. These tests include, besides pure tone audiometry, air and bone, discrimination tests, impedance audiometry, tests for recruitment and diplacusis, etc. A diagnosis of Meniere's disease *cannot* and should not be made without appropriate audiometric findings Tinnitus, dizziness, and hearing loss may mean Meniere's disease, but they may also mean an acoustic neuroma.
5. Optokinetic nystagmus — This occurs normally when we watch a succession of moving objects, as from a train window. We can simply use a tape measure for the test, holding it 18 inches from the eye, and moving it across the field of vision with the head immobile. Or we can use a rotating striped drum and nystagmographic tracings. If no nystagmus should occur, we think of a visual field defect due to cerebral disorders. Normally, the slow component of the nystagmus is in the direction of the moving object.
6. Water caloric test — This should only be done when the patient has an intact eardrum; otherwise, *active otitis media will occur*. 2 cc. of ice water are injected slowly with the patient's head held back and to the side. Quickly empty the ear of water in 20 seconds and tilt the head back 60 degrees from the vertical. Observe the nystagmus, its frequency, and the length of time it lasts. The fast component, when cold water is used, should be to the opposite ear. You compare the reaction in both ears after waiting approximately 10-15 minutes between testing each ear. Ask the patient if the sensations are similar to those he experienced when he suffered his spontaneous vertigo. If so, this would be very suggestive of a peripheral source of his problem. A reduced or absent caloric is seen in acoustic neuroma. Meniere's disease may or may not show a reduced response. Vestibular neuronitis will show a reduced or absent response. Psychogenic cases usually exhibit a hyperactive response.
7. Xrays — These may include mastoid Xrays to rule out mastoid disease, tomography to determine size of the internal auditory canal on each side. This rules out an auditory canal stenosis or a possible acoustic neuroma within the canal; clivograms, to rule out an acoustic neuroma in the posterior fossa; EMI scan can also be most helpful here. Angiography, in my opinion, should only be done when ordered by a neurologist. Xrays of the cervical spine are ordered if you have reason to suspect intermittent vertebral artery occlusion due to cervical osteoarthritis.

Meniere's Disease

History: Episodic vertigo Fluctuating hearing loss (aural pressure can come and go)

Tinnitus — from seashell type to a whole cacophony of sounds

Vertigo rarely lasts longer than a day

Neuro-otologic Findings:

Tuning forks show sensorineural hearing loss No cranial nerve involvement

Caloric test may be normal or reduced response

Audiometry will show diplacusis, recruitment, absence of tone decay

X-rays: Negative

Laboratory: Normal

Treatment:

A. Medical: (1) reassurance (2) drugs (3) antivertiginous drugs such as Tigan, Dramamine, Marezine

B. Sedatives or tranquilizers — often antihistamines help, particularly in an already allergic patient

C. Use of vasodilator drugs such as Nicotinic Acid. They give the patient good flush, and this often makes them feel better.

D. *Rest, quit smoking*, diet, overweight. Refer for complete evaluation if allergy or thyroid imbalance is suspect.

Acoustic Neuroma

Unilateral tinnitus and hearing loss (Bilateral, very rarely, eg., multiple neurofibromatosis)

Positional imbalance often present rather than true vertigo. Hearing loss may be sudden. Patient may complain of pulling feeling in neck behind involved ear.

Tuning forks show sensori-neural hearing loss.

May show involvement of V and VII cranial nerves as shown by loss of corneal reflex or by loss os stapedial reflex.

Caloric test reduced or absent response

Audiometry may show incomplete recruitment and presence of tone decay

Positive for acoustic neuroma (May need a clivogram to demonstrate it)

Laboratory may be normal

Surgical removal

Surgical:

In rare cases where patient cannot function because of vertigo and where hearing loss is unilateral, *decompression* is done (shunt procedure). Also, central vestibular nerve sections have been done with good results.

Vestibular Neuronitis

History:

Usually follows flu or URI. Onset sudden and violent, associated with nausea and vomiting. Can last days or weeks. Often seen in "pocket epidemics", occurs at any age.

Time Period:

Usually clears in several weeks, but lightheadedness may persist for six months.

Involvement of Other Cranial Nerves: No

Caloric Test Findings: Reduced caloric on involved side

Benign Positional Vertigo

History:

Onset sudden and associated with assumption of provocative head positions. With positional testing, there is often a *latent* period before onset of the vertigo or nystagmus. Repetition of the test position fatigues the reaction. Vertigo recedes after 15-20 seconds.

No tinnitus

No hearing loss

Usually occurs in people over 45 years of age

Time Period:

Usually clears in several months. Most always will recur at a future time. Patient should be forewarned for purpose of reassurance.

Involvement of Other Cranial Nerves:

No

Caloric Test Findings:

No reduced caloric on either side

Basilar Vertebral Syndrome

History:

Onset sudden with drop attack

Last but a few seconds.

May have had other associated complaints (the D's).

May have history of ossicular disease

Ear findings normal for age

Time Period:

Often gets worse with time, increasing in frequency and severity.

Involvement of other Cranial Nerves:

Yes

Caloric Test Findings: No reduced caloric on either side

Suspect Central Causes When:

1. Consciousness is lost
2. History of cancer or vascular disease
3. Spontaneous vertical nystagmus is present or elicited
4. Positional nystagmus occurs with eyes open and yet *no* associated vertigo occurs
5. Vertigo is present and caloric and ENG findings are unremarkable
6. Optokinetic nystagmus does not follow the usual pattern
7. Audiological findings, nystagmogram, and x-ray findings suggest a fossa tumor
8. In young individuals presenting with vertigo and/or tinnitus and with no auditory findings — suspect M. S.

Suspect Peripheral Causes:

1. When hearing changes and tinnitus are associated with the vertigo
2. In cases where a true substantial vertigo occurs very similar to that produced with caloric stimulation
3. Where middle ear or mastoid disease is present and fistula test is positive
4. Where positional vertigo is present with a demonstrable latent period and fatigability response
5. Where a typical Meniere's history (fluctuating hearing loss, tinnitus, episodic vertigo) is present associated with typical audiological findings — low tone sensori-neural loss, diplacusis, recruitment, absence of tone decay
6. Sudden hearing loss and vertigo caused by viral disease (measles or mumps)
7. Vertigo associated with trauma and history of blood coming out of external ear canal — indicating a basal skull fracture and probable labyrinthine injury
8. Sudden hearing loss and vertigo occurring with severe strain and elevated C.S.F. pressure (eg. blow on abdomen, lifting heavy objects). This can cause a round window membrane rupture, which if suspected, should be repaired quickly.

When Should you Refer Your Patient?

1. When you discover a unilateral sensori-neural hearing loss
2. Patients with more than one attack of vertigo that simply "doesn't fit in pigeon hole"
3. Patients who require Gentamycin or Streptomycin therapy, particularly when their kidney function is NOT TOO GOOD. Both drugs are vestibulo toxic, and serial vestibular function tests should be done.
4. Patients who do not recover within a time period you would expect
5. Patients with findings suggestive of C.N.S. involvement

The Cardiovascular System and Dizziness

Robert Van Tassel, M.D.*

The subjective complaint of dizziness may have its origin in any one of multiple disease states that may affect the cardiovascular system. A careful history and physical examination will generally suffice to clairfy the underlying problem and appropriate therapy may be initiated. However, not infrequently additional cardiac studies are necessary to more precisely define the problems. These studies include chest Xray, electrocardiography, echocardiography, and rarely cardiac catheterization.

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*Clinical Associate Professor, Department of Medicine, University of Minnesota, Minneapolis.

Both system hypertension and hypotension (usually orthostatic) may present with the initial complaint of dizziness. The history and physical examination are generally diagnostic in this condition.

Atherosclerotic heart disease may present clinically with congestive heart failure, cardiac dysrhythmias, heart block, or coronary insufficiency all of which may be manifested by the subjective symptom of dizziness.

Valvular heart disease and congenital heart disease may give rise to dizziness by limiting the appropriate increase in cardiac output with exercise.

In atherosclerotic, congenital, and valvular heart disease additional cardiac studies are frequently necessary to implicate the underlying disease as the etiology of the patients complaint of dizziness.

Ambulatory monitoring of the electrocardiogram has been a significant technilogical advance which only recently has been routinely utilized clinically. It has extensive application in the evaluation of the patient presenting with the complaint of dizziness where no obvious etiology is readily apparent.

MMA ANNUAL MEETING MAY 17-18, ST. PAUL

This year in St. Paul, the MMA Annual Meeting is planned to show you more of the city than the inside of the headquarters hotel, Radisson St. Paul. Twenty-five accredited courses in continuing medical education are offered. In addition to small seminars, lectures and panel discussion courses, there are skills workshops hosted by some of the local hospitals where registrants may use laboratory facilities unavailable in a hotel setting.

The MMA House of Delegates meets on Wednesday May 16 at the Radisson, followed by a reception opening the exhibits, two days of scientific program, the Annual Luncheon, the President's Reception and Banquet, and several specialty society meetings. The MMA Auxiliary offers a full schedule of events for spouses throughout the meeting.

Golfers and tennis buffs have the usual opportunity to visit the host city's greens and courts, and this year runners may compete in two races added to the athletic events schedule.

Extensive planning and preparation are responsible for the largest scientific program ever offered at the MMA Annual Meeting. The Medical Education Subcommittee on Scientific Assembly invites you to attend and take advantage of this fine selection of courses.

Registration materials are scheduled for mailing in February. For further information contact:

CME Department
Minnesota Medical Association
900 American National Bank Building
St. Paul, Minnesota 55101

S. V. Thorson M.D.
Chairman
MMA Subcommittee
on Scientific Assembly

American Diabetes Association of Minnesota

5400 Glenwood Ave. No.
Minneapolis, Mn. 55422
612-546-9619

Chapters

Duluth Chapter
Daryl Jakubek, President
2040 Howard Gnesen Road
Duluth, Mn. 55803
218-721-3410

Rochester Diabetes Assn.
Gloria Brower, President
5608 Chateau Road
Rochester, Mn. 55901
507-289-5433

Twin Cities Diabetes Assn.
Donna Hill, Executive Director
5400 Glenwood Ave. No.
Minneapolis, Mn. 55422
612-546-8906

Branches of TCD

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Janet Gratz
16048 Lester Avenue E.
Hastings, Mn. 55033
612-437-7404

Eastern Metro St. Paul Branch
Kenneth Hassler
690 East Hoyt
St. Paul, Mn. 55106
612-776-2669

North Suburban Branch
Robert Blum
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Coon Rapids, Mn. 55433
612-421-3184

Units of ADAM

Arrowhead Diabetes Assn.
Michael Novak
510 S. Central
Chisholm, Mn. 55719
218-254-5582

Austin Diabetes Association
Sid Brown
1315 6th Ave. NW
Austin, Mn. 55912
507-433-2680 — home
507-437-6631 — work

Big Stone Diabetes Assn.
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337 Oson
Ortonville, Mn. 56278
612-839-2877

Blue Earth-Nicollet Co.
Ron Cey
416 Wheeler
North Mankato, Mn. 56001

Central Minnesota Diabetes Assn.
Hans Engman, M. D.
1624 Calvary Hill Lane
St. Cloud, Mn. 56301

Carlton County Unit
Shirley Ahiers
609 Walnut Street
Cloquet, Mn. 55720
218-879-8876

Clara City Diabetes Assn.
Delwin Schwitters
Box 21, RR 1
Clara City, Mn. 56222
612-847-2160

Crow Wing Diabetes Assn.
Karina Hoversten
1416 S. 6th
Brainerd, Mn. 56401
218-829-5262

Fairmont Diabetes Assn.
Juleen Grefe
Fairmont Medical Clinic
800 Clinic Circle
Fairmont, Mn. 56031
507-238-4263 — work
507-238-1103 — home

Itasca County Diabetes Assn.
Ken Lundgren
1605 6th Avenue SE
Grand Rapids, Mn. 55744
218-326-3482 — work
218-326-1093 — home

Jackson County Chapter
Mn. Diabetic Assn.
Mrs. Beverly Peterson
Route 1
Jackson, Mn. 56143
507-847-4653

Kanabec County Diabetes Assn.
Barb McGuire
RR
Mora, Mn. 55051
612-679-3592

Lac Qui Parle Diabetes Assn.
Carol Femrite
RR 3, Box 177
Dawson, Mn. 56232
612-752-4468

Marshall Area Unit
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228 N. Whitney
Marshall, Mn. 56258
507-532-2416 — home
507-532-9631 — work

Meeker Co. Diabetes Assn.
Karen Nelson
1002 S. Armstrong
Litchfield, Mn. 55355
693-6364

Montevideo Diabetic Club
Virgil Lange
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Montevideo, Mn. 56265
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Morris Area Diabetes Assn.
Maggie Fletcher
RR
Morris, Mn. 56267
612-589-1313

New Ulm Area Diabetes Assn.
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New Ulm, Mn. 56073
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Northeastern Diabetic Club
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Ely, Mn. 55731
218-365-4232

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404 South Court St.
Fergus Falls, Mn. 56537
218-736-3591

Pipestone Unit
Don Lein
Box 145
Pipestone, Minnesota 56164
507-825-5534

Rainy Lake Diabetes Assn.
Gwen Bender
1324 10th St.
International Falls, Mn. 56649
218-283-8933

Redwood Co. Diabetes Assn.
Karen Jones
Route 1
Redwood Falls, Mn. 56283
507-637-3163

Renville County Diabetes Assn.
Inez Kienholz
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Bird Island, Mn. 55310
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Slayton, Mn. 56172
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Waseca, Mn. 56093
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319 Second Ave. SW
Forest Lake, Mn. 55025
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Swift County Diabetes Assn.
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Benson, Mn. 56215
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Upper Hiawatha Valley Diabetes Assn.
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1747 Spruce Place
Red Wing, Mn. 55066
612-388-6605

Willmar Area Diabetic Club
Don Eberlein
1104 East 2nd Street
Willmar, Mn. 56201
612-235-1970

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William Sillman, Chairman
1002 W. Howard
Winona, Mn. 55987
507-454-6280

Worthington Area Unit
Alan Truckenmiller
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American Diabetes Association Minnesota Affiliate
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Minneapolis, Minnesota 55422

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___ Please enroll me as a member of ADAM.
    ___ First year dues of $12.00 enclosed.
    ___ Please bill me for dues.
___ Please send information regarding educational materials available.
___ Please notify me of professional educational programs in my area.
___ Other ____

Classified Advertisements

Classified advertising rates are forty (40) cents a word; minimum monthly charge $10.00, key number, $1.50 additional Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 101 East 5th, Suite 900, St. Paul, Minn. 55101.

Group of 70 physicians in Phoenix, Arizona in need of Family Practitioners, Ophthalmologist, Pediatrician, OB-Gyn, Anesthesiologist, Psychiatrist, Internist, Gastroenterologist and Surgeon-General Vascular/Thoracic; Excellent working conditions, salary and benefits; Ideal living conditions. Write Medical Director, Health Maintenance Associates, Ltd., 4747 No. 22nd Street, Phoenix, Arizona 85016 or call (602) 957-9200, Ext. 355.

For sale: General/Family Practice, Northwest Minneapolis Suburb. Established 22 years. All records and equipment, X ray and E.K.G. included. Assume lease. Terms. Write MINNESOTA MEDICINE Box 539, 101 E. 5th St., St. Paul 55101 or call collect 612-588-6401.

Two family practitioners urgently needed to join established group in one of the fastest growing areas of western Wisconsin. Ideal mix between farming, industry and outdoor recreational and resort area, short drive by freeway to Minneapolis and St. Paul. 84 bed J.A.H.A. approved hospital and nursing home complex. Salary $40,000+, full partnership after a year, without investment. Contact Richard L. Hartzell, M.D., Grantsburg Clinic, Ltd., Box 169, Grantsburg, Wisconsin 54840 (715-463-5317) or Frank Snapp, Administrator, Burnett General Hospital, Grantsburg, Wisconsin (715-463-5353).

Wanted: family physician — to join two Board Certified Family Physicians and a Certified Physician Assistant in a Southwestern Minnesota community of 4,500. Please contact either Doctors Dokken or Johnson at the Windom Clinic, Ltd., 1041 3rd Avenue, Windom, Minnesota 56101 or phone AC507-831-2550.

Family practice, internist, OB-GYN, General Surgeon, and Orthopedic Surgeon needed for multispecialty group with Family Practice Dept. in Crookston, Minnesota. Located in heart of the Red River Valley, stable economy, good income, new clinic facility, full member in one year. Contact R. F. Schnabel, M.D., 218-281-3184, Crookston, Minnesota.

Residency training programs in preventive medicine and in occupational medicine. Unique programs in preventive medicine-internal medicine and in occupational medicine-internal medicine have been developed at Mayo Graduate School of Medicine. Principal objective of the preventive medicine program is to train physicians expert not only in internal medicine but also in clinical preventive medicine, blending general medical care expertise with competence in applied epidemiology, health care systems planning, evaluation of effectiveness of health care systems, and health care quality assessment. Prerequisites for the preventive medicine program include 24 month's hospital-based training in internal medicine either at Mayo Clinic or other approved institutions. Program components include 12 months of full-time didactic study leading to an M.P.H. degree, one year of junior residency training in clinical preventive medicine, and one year of advanced training which is planned in accordance with the talents and interests of the resident. A research fellowship year is optional.

The occupational medicine residency, funded by the NIOSH Centers Program, is designed to train physicians in both internal medicine and occupational medicine to be qualified for appointment in major academic medical centers as clinicians, teachers and investigators, or for appointment as staff members of corporate medical departments of major institutions, or for positions in departments of public health. Components of the occupational medicine program include three years of study in internal medicine, one year of study leading to an M.P.H. degree, and one year of advanced study in occupational medicine. An additional optional year as a research fellow is available.

Entry at various levels of training programs may be possible if suitable clinical and/or academic training has been obtained previously.

As residents progress through these programs, they will become eligible for examination by both the American Board of Internal Medicine and the American Board of Preventive Medicine.

Inquiries should be addressed to Earl T. Carter, M.D., Ph.D., Division of Preventive Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota 55901.

Mayo Foundation is an Equal Opportunity/Affirmative Action Institution.

(Continued on Page 68)

(Continued from Page 67)

THIS IS A UNIQUE, and challenging opportunity for a Family Practitioner to develop and expand a central department of Family Practice with peripheral satellites for a multispecialty group in North Iowa. Strong support from the other specialties including Internal Medicine, Surgery, Ob/Gyn, Allergy, and Dermatology is available. Attractive community of 32,000 serving needs of 200,000 area citizens. Convenient to Minneapolis, Mayo Clinic, and Des Moines via I-35. Eight miles to Clear Lake "Iowa's Vacation Capitol". New office building-hospital complex (August, 1978). Second hospital in community newly remodeled and expanded. Teaching opportunities. Partnership after one year. Salary generous. Vacation and Study Time. Pension Plan program. For more information, please mail your curriculum or call collect AC 515-423-4120, and ask for the "Info Pack" from Park Clinic, 116 No. Washington Ave., Mason City, Iowa 50401.

APPLICATIONS WELCOMED from board-qualified or certified radiologists, large teaching hospital, upper Midwest; university affiliation, subspecialty training in pediatrics and/or therapy desirable. Box 529, MINNESOTA MEDICINE, 101 E. 5th St., St. Paul 55101.

INTERNIST AND FAMILY PHYSICIANS wanted by 10 person medical group in Alexandria, Minnesota. Please contact Paul H. Engebretson, M.D., 610 Fillmore, Alexandria, MN 56308. Telephone: (AC612) 763-5123"

PHYSICIANS — Metropolitan Medical Placement offers assistance through our no obligation to the physician placement service. We always have several active listings throughout Minnesota and we specialize in *aggressively* seeking our opportunities to match each physician's individual needs. If you desire confidentiality and professionalism in our search efforts, then we ask you please to contact Mr. Holmes at 612-831-5232.

FAMILY PRACTITIONERS needed immediately to join present three physicians corporate group practice in rural Southwestern Minnesota; guaranteed income with liberal fringe benefits; full partnership after one year; no investment necessary; new clinic facility attached to newly renovated hospital; area offers excellent recreational activities; top school systems; warm community atmosphere. Contact J. L. Bader, M.D., Chief of Staff, Slayton Clinic, 2744 Broadway Avenue, Slayton, MN 56172; Phone number: (507) 836-6153 or 836-6463.

46 YEAR OLD, no smoke, no alcohol, serious runner, GP/FP desires younger associate with same interests and philosophy. 60 year old, established, very successful, general medical/family incorporated practice. High work motivation/medical interest necessary. Married/children preferred. Small town lifestyle/30 miles from Mpls./St. Paul, Minn. Respond with particulars to Box 9812, Mpls. P.O., Mpls., Minn. 55440. All respondents will be contacted.

ENT, OPHTHALMOLOGY, FAMILY PRACTICE and CARDIOLOGY specialty positions available with Mankato Clinic, Ltd. Our 30 man multi-specialty group attracts specialty referrals from a Southern Minnesota area of 250,000 population. Excellent group practice opportunity in All-American community with full hospital services; full range of group fringe benefits; liberal time off; salary first year; incentive pay thereafter. For more information call collect R. F. Roskens or Dr. B. C. McGregor, 507-625-1811.

GENERAL SURGEON, OB-GYN, INTERNIST, FAMILY PRACTITIONER — To join growing eleven physician primary care clinic, located in a stable, economically sound, family oriented community on the threshold of Minnesota's wilderness area. New 175 bed hospital under construction. Excellent compensation including medical, Life, A-D&D, disability insurance, pension, profit sharing, continuing education reimbursement, liberal vacation, etc. Contact Bayard French, M.D. or Jack Davis, Administrator c/o Adams Clinic, P.A. 2229 E. 3rd Ave. Hibbing, Minnesota 55746 Telephone (218-262-3425).

FAMILY PHYSICIAN wanted to join active practice with two family physicians and general surgeon. Generous starting salary with a full range of benefits. Located one hour southwest from Twin Cities. Growing community with excellent recreational and educational opportunities. New clinic with community hospital nearby. Contact: Jo E. Anderson, M.D. or Duane R. Schultz, Business Manager, Minnesota Valley Medical Associates, 301 Valleygreen Square, Le Sueur, Minnesota 56058. Phone (612) 665-3391.

INTERNIST — age 33, certified, seeking position with clinic or private practice. Call Dr. Robert Korchik, 4124 Gettysberg Ave. North, New Hope 55427. Phone: 533-2285.

Classified Advertisements

THE FARIBAULT CLINIC, LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

12 PHYSICIAN, multi-specialty clinic needs an Ob-Gyn. Ours recently retired. The present group includes general surgeons, internists, a urologist, an ophthalmologist, an otolaryngologist and family practitioners. Northeastern Minnesota location with complete hospital facilities. Excellent recreation country, both summer and winter. Solid and growing economic conditions. No big city problems. Please call collect relative to any questions. Reply — Mesaba Clinic, Hibbing, MN 55746 or call John Brust at (218) 262-3441.

Three year approved Psychiatric Residency Program now appointing for an immediate unexpected opening and for July, 1979. Small intensive psychiatric hospital, JCAH approved, affiliated with University of Iowa Medical College. Comprehensive program including two adult psychiatric units, adolescent unit, childrens unit, alcohol & drug abuse unit, with innovative community liaison, and OPD. Eclectic approach. Situated in picturesque northeast Iowa near large cities with cultural advantages, but in rural setting. Ideal for family living. No financial sacrifice while learning. Top salary: first year $23,478, second year $24,648, third year $25,896; liberal fringe benefits; some housing available. Opportunity to join staff upon completion of training. All applicants must have completed one year in an American approved training program in internal medicine, family practice, or pediatrics or a flexible one year program, including four months in internal medicine. Wirte or call J. T. May, M.D., Superintendent, or B. J. Dave, M.D., Director of Education, Mental Health Institute, Independence, Iowa 50644.

Psychiatrists—GP's — Openings at State Hospitals in Fergus Falls, Rochester, St. Peter and Willmar. Salary $30-45,000, plus liberal fringe benefits. Call Ronald Young, M.D., Dept. of Public Welfare (612/296-3058).

Internal medicine, orthopedic surgeon, and family practitioner to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities; starting salary $40,000 per year. Contact Personnel Director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611.

Family practice physician: — To Join: 7 man Family Practice Group. Complete call system, new clinic (10,000 sq. ft.). New accredited 65 bed hospital and adjacent 100 bed nursing home. Serves area of 10 to 12,000 people in active stable community. Located in the heart of northern recreational area. Contact F. H. Walter, M.D. or George M. Crow, M.D. at the Falls Medical Center, P.A., Box 791, Shorewood Drive, International Falls, Minnesota 56649; Telephone: (218) 283-9431.

Position wanted: Psychiatrist — 20 years experience in out patient and inpatient therapy and consultant work seeks consultative work in Minn. or part-time private practice on percentage or salary basis. Write: MINNESOTA MEDICINE — 540 101 E. 5th St., #900 St. Paul 55101.

Psychiatric residency: Immediate vacancies for PG2 through PG4 through July 1, 1979. Those eligible for an Iowa Residents license via the ECFMG receive stipends of: 1st year, $21,294; 2nd year, $22,360; 3rd year, $23,478. Those eligible for a regular Iowa license vie FLEX or reciprocity receive stipends of: 1st year, $23,478; 2nd year, $24,648; 3rd year, $25,896. T. B. McManus, M.D., Superintendent, Mental Health Institute, Cherokee, Iowa 51012. Call Collect 712-225-2594. Equal Opportunity Employer.

Wanted: psychiatrist for Mental Health Center and/or private practice Northwest corner of state. Center desires additional psychiatrist in area. Will either guarantee development of private practice, or full time position with the Center or combination. Excellent salary and fringe benefits. Delightful professional staff developing innovative programs in the seven county area. A professionally exciting opportunity. Contact Roy Waters, Executive Director, Northwestern Mental Health Center, College Avenue, Crookston, MN 56715. Phone: area code (218) 281-3940.

(Continued to Page 70)

(Continued from Page 69)

PHOTOGRAPHY/SKIING: NATURE PHOTOGRAPHY AMERICA, direction Charles Steinhacker, Richard Smith, well known nature photographers, conducts weekly workshops. Join a uniquely successful nature photography approach with exhilarating outdoor experience. Splendid opportunity for creativity amidst incomparable surroundings. NPA, Telemark Lodge, Cable, WI 54821. 715-798-3811.

FAMILY PRACTITIONER — Internist — 14 man mixed Family Practice Speciality Group with a modern clinic wishes to add an additional Family Practitioner and Internal Medicine Doctor. Have one satellite office. Modern hospital one block from Clinic. Desirable community with excellent school system. Good salary and wide range of fringe benefits. Contact Thomas A. Treanor, M.D., Albert Lea Medical and Surgical Center, Ltd., Albert Lea, Minnesota, Phone 373-1441 or 373-3051.

WANTED: PSYCHIATRIST for Mental Health Center and/or private practice Northwest corner of state. Center desires additional psychiatrist in area. Will either guarantee development of private practice, or full time position with the Center of combination. Excellent salary and fringe benefits. Delightful professional staff developing innovative programs in the seven county area. A professionally exciting opportunity. Contact Roy Waters, Executive Director, Northwestern Mental Health Center, College Avenue, Crookston, MN 56716. Phone: area code (218) 281-3940

SUBURBAN MINNEAPOLIS: Opening in early 1979. 3-man Family Practice Group (PA) is looking for a replacement for a member entering the teaching field. Salary and Bonuses. Own lab & X-ray, 600-bed hospital with complete facilities and consulting staff a few blocks away. Call collect — or write to: Robbinsdale Clinic, PA, 3819 West Broadway, Robbinsdale, Minn. 55422. ATTN: Donald D. Metz, M.D. (612) 533-2534.

15 DOCTOR MULTISPECIALTY group is looking to add two doctors in the Family Practice Dept.; one doctor in orthopedic surgery, internal medicine and OB/GYN. Recreational, educational and cultural opportunities abound in small town atmosphere of northern Minnesota. New clinic and hospital under construction. Contact D. E. Carlson, Bemidji Clinic, Bemidji, MN 218-751-1280

PHYSICIAN'S ASSISTANT, 26, National certification, Family Practice and General Surgery Experience, Prefer Twin Cities and suburbs. Gary Stepan, 741 E. Jessamine, St. Paul, Mn. 55106, (612) 7762000.

ATTENTION RUNNERS: Athletic events at the MMA Annual Meeting aren't just for golfers and tennis players anymore. Two races are scheduled for Wednesday morning, May 16 in St. Paul. Watch for details in Annual Meeting registration materials.

What's new in St. Paul? The Science Museum of Minnesota, Landmark Center, Lowry Arcade, Summit Hill Restoration, Smith Park Redevelopment, Mears Park Apartments, Victoria Crossing . . . If you haven't been there since 1975, it's time for another visit. MMA Annual Meeting, May 17-18, Radisson St. Paul.

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

ROCHE

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days

- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice
- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

ROCHE

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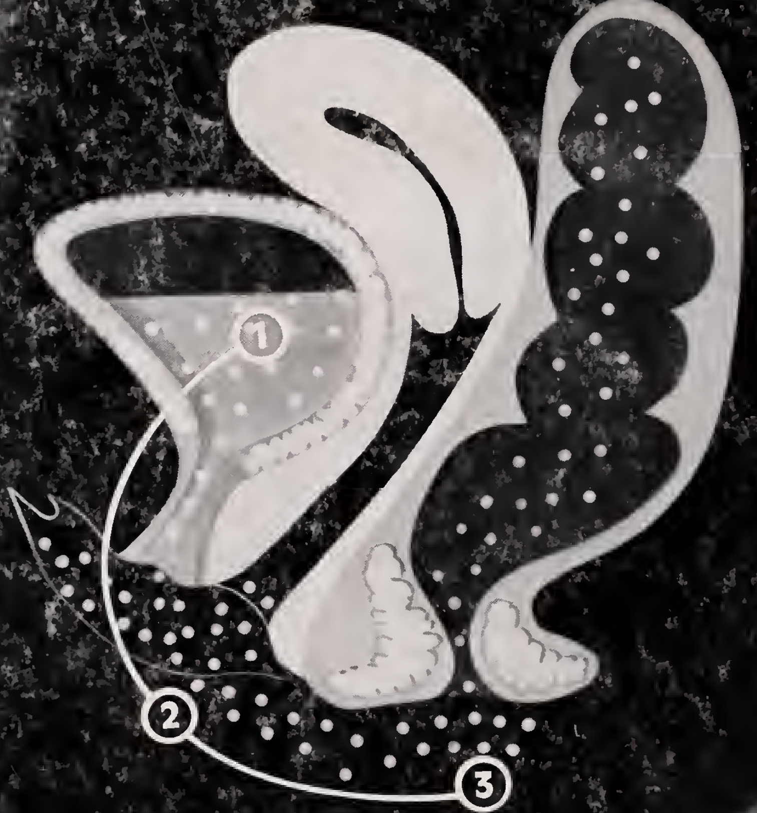
Please see back cover.

Her next attack of cystitis may require

the Bactrim™ 3-system counterattack



Library College of Physicians
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Philadelphia, PA 19103

ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

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Contents — February, 1979

COVER WATERCOLOR — "Minneapolis Skyline"
E. Theodore Palm, M.D. ... 106

PRESIDENT'S LETTER — Health Care Cost Commission Report
Robert S. Flom, M.D.
President, Minnesota Medical Association ... 75

EDITOR'S NOTEBOOK — thrrree rrr s
minny ... 77

EDITORIAL — Twenty-five Years of Psychopharmacology
F. S. Abuzzahab, Sr., M.D.
Guest Editor ... 79

ORIGINAL CONTRIBUTIONS

Chlorpromazine's Entrance into Psychiatry — An Extremely Interesting Product
Judith P. Swazey, Ph.D. ... 81
Psychopharmacology and Family Practice
Harley Racer, M.D. ... 91
Impact of Depot Neuroleptics on Psychiatry
Lionel Corbett, M.D. ... 97
Parkinson's Disease, Huntington's Disease and Tardive Dyskinesia — Neurochemical Pathology and Treatment
Eduardo S. Tolosa, M.D. ... 101
Impact of Psychotropic Drugs on Research in Psychiatry
John M. Davis, M.D. and Maurice W. Dysken, M.D. ... 109

SPECIAL ARTICLE — The Case for "Brain Death" Legislation — A Response to the Critics
William H. Manning, J. D. and Howard J. Vogel, J. D. ... 121

RHEUMATOLOGY CORNER — Natural Course of Rheumatoid Arthritis
Roger Colton, M.D. ... 129

MINNESOTA MEDICAL ASSOCIATION — Syllabus

Recognition and Care of the High Risk Pregnant Patient and Neonate
Jack L. Strobel, M.D., Moderator
Management of Labor in the High-Risk Patient ... 133
and
Prenatal Detection of Genetic Diseases
Richard P. Bendel, M.D. ... 135
Annual Meeting
S. V. Thorson, M.D., Chairman
MMA Subcommittee on Scientific Assembly ... 80

CONTINUING MEDICAL EDUCATION — Farewell Old QACME
J. S. Welch, M.D., Chairman
Medical Education Committee, MMA ... 137

Q and A — CME
J. C. Cain, M.D.
Chairman, Continuing Medical Education Committee of the Minnesota State Board of Medical Examiners ... 85

MINNESOTA STATE BOARD OF MEDICAL EXAMINERS ... 95

CONTINUING MEDICAL EDUCATION LISTINGS ... 80, 85, 100, 127, 140

CLASSIFIED ADVERTISING ... 128

INDEX TO ADVERTISERS ... 120

Volume 62:2
Pages 71-140

MINNESOTA
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President's Letter

Health Care Cost Commission's Report

It is anticipated that the next issue of MINNESOTA MEDICINE will carry the final report of our Cost Commission. Although the final report of the Commission and the comments of its members, as of the time of this writing, are not as yet available, certain characteristics of its expected content may be anticipated.

The only sure anticipation, which may be stated, is that the report will please no one completely. Also certain is the assumption that parts of the report will please everyone as he or she views it from his or her own perspective. Its contents should shed some light upon how other segments of society view us, which should be of value to all of us.

The Commission, composed of community leaders, was established as a result of an action taken by the Board of Trustees of the Minnesota Medical Association subsequent to the reorganization of the Association which suggested a lay advisory board be formed.

It was apparent that one of the most crucial concerns which needed to be addressed by the Association was cost containment, and that we needed advice in this area. In a larger and more important sense the public, also, needed advice from a free standing commission which would create and own its own report.

The Cost Commission members served at our request, represented a large segment of society known to be knowledgeable in this area and served diligently and voluntarily over an eighteen-month period. The members brought forth their own views on how the health care system served society and how it could be reshaped to more cost effectively serve the public need.

Some came to see physicians' problems and the reasons for certain policy postures with more perspicacity, and, I believe, the report will make it possible for physicians to understand better the problems our patients and their payors of premiums and benefit dollars face as medical care becomes rapidly more complex and comparably costly.

It can be expected that the Cost Commission will stress heavily incentives for cost containment on the part of physicians, medical care institutions, third party carriers, and the consuming public. It will urge government restraint in its attempts to manage by fiat factors which are symptoms, while such management really compounds the ailment. Cost consciousness on the part of physicians will receive considerable attention.

Many of the suggestions contained in the report many appear obsolete, since rapid changes are going on already in the health care delivery system. Whether or not the report has major impact on health care costs depends upon our acceptance of the principles contained therein, our willingness to act upon the suggestions, and in the final analysis how history views the wisdom and practicabilities of the recommendations.

It will, in any event, represent the considered judgment of many knowledgeable people who have made a major commitment and worked diligently, arriving at their conclusions by a democratic process.

Robert S. Flom

Robert S. Flom, M.D.
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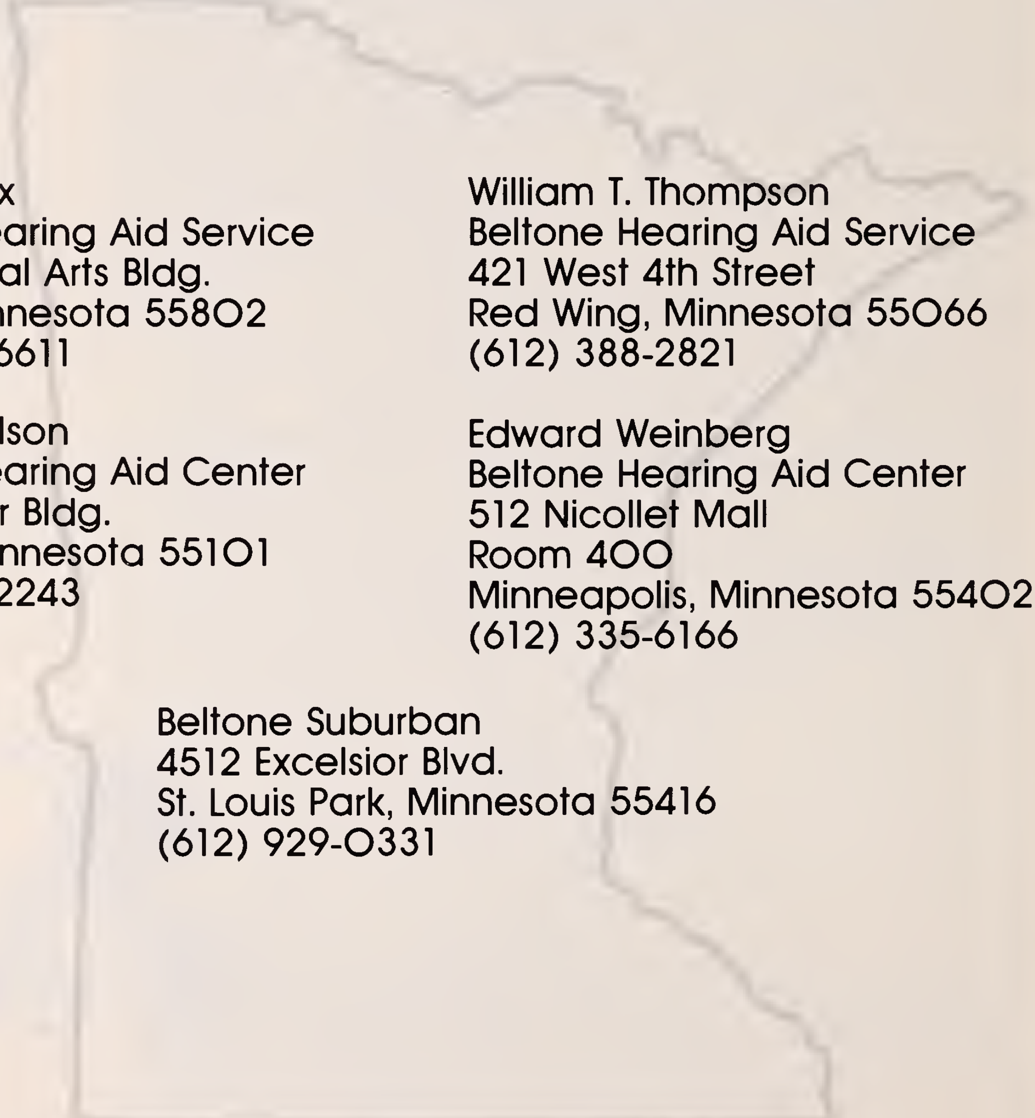

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Editorials

Twenty-five Years of Psychopharmacology

F. S. ABUZZAHAB SR., MD, PhD.*

Guest Editor

AS A NAIVE COLLEGE student visiting a state hospital in 1952, prior to the introduction of psychoactive drugs as part of a course in abnormal psychology, I would not have believed that these wards would be one day emptied and the institution possibly completely closed. The impact of psychoactive drugs on institutionalized psychiatric patients has been world wide. The drastic reduction of the patients requiring inpatient hospitalization has been in large measure due to the effective application of psychoactive medication.

This silver anniversary of the introduction of chlorpromazine by Delay and Deniker in 1952[1] in France was celebrated by a symposium co-sponsored with the Minnesota Academy of Family Practice, June 4, 1977. The papers from this symposium are organized for two issues of Minnesota Medicine. This issue will cover the neuroleptics and the second issue will include the antidepressant and antianxiety agents.

A nationally known speaker, Judith P. Swazey, Ph.D.,† who has been commissioned by the Committee on Brain Sciences, Division of Medical Sciences, National Research Council, to write *Chlorpromazine in Psychiatry, A Study of Therapeutic Innovation*[2] will depict the story of the introduction of chlorpromazine.

Not only are the psychiatric hospitals empty thanks to psychoactive drugs, illustrated by the closing of Hastings State Hospital, Hastings, Minnesota, on May 1, 1978, but a silent and yet interesting phenomenon has occurred. Psychiatric patients can now be managed by their primary care family physicians. Dr. Harley Racer‡ will review the impact of psychotropic drugs on the Family Practice scene.

The introduction of depot phenothiazines in the form of fluphenazine esters, both the enanthate and decanoate, has increased the successful application of neuroleptics. Clinicians are now able to reach therapeutic levels in patients who were otherwise uncooperative or unreliable about their oral medications, or have a poor result due to quick metabolism or poor absorption of oral medications. Dr. Lionel Corbett° will review the impact of depot phenothiazines in psychiatry, which has led some physicians to feel that if a psychosis does not respond to depot phenothiazines, it might not respond to neuroleptics at all.

The long term effects of neuroleptics as manifested in tardive dyskinesia brought into psychiatry the dilemma of clinical pharmacology in general. Most drugs are introduced for their acute effect. When they are used over a long period for chronic diseases such as schizophrenia, some unpredictable long term side effects emerge, such as tardive dyskinesia. Current trends in the treatment of extrapyramidal disorders will be the topic of Dr. Tolosa's§ address.

Since it is a basic tenet of pharmacology that a drug cannot produce an effect unless the organism has the capacity to produce that effect without the drug, psychoactive drugs which were discovered empirically in the clinic became tools in the hands of the basic and clinical psychopharmacologists to unlock the secrets of the brain. Therefore, it is appropriate to ask Dr. John Davis# to review the impact of psychoactive drugs on research in psychiatry.

Through the introduction of chlorpromazine in schizophrenia, Kuhn discovered the antidepressant property of imipramine when he was searching for a better antipsychotic in schizophrenia.[3] The second issue of the symposium papers will cover the treatment of affective disorders, the use of benzodiazepines in outpatient treatment, and the status of the Food and Drug regulation of clinical psychopharmacology.

As president of the Hennepin County Psychiatric Society, I would like to share with you how my own professional life has been highly influenced by the psychoactive drugs. Although our textbook, the second edition of Goodman and Gilman[4] had a passing reference to chlorpromazine, its impact was felt worldwide.[5,6] As I was starting my rotating internship after medical school, the first Collegium Internationale Neuropsychopharmacologicum was held in Rome in 1958.[7] As a participant, I was further moved by the address of Pope Pius XII to the Collegium members, with chlorpromazine receiving his papal blessing.

---

*Clinical Associate Professor, Departments of Psychiatry, Pharmacology and Family Practice, University of Minnesota Hospitals, Minneapolis, Minnesota.

Presented at the Symposium on 25 Years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

†See page 81.
‡See page 91.
°See page 97.
§See page 101.
#See page 109.

My decision to pursue the Ph.D. in Pharmacology at the University of Minnesota was highly influenced by the impact of these drugs on the general practice of psychiatry.

I want to take this opportunity to express my deep gratitude to Ms. Mary Sherman, my executive assistant, without whose energy and support this meeting would not have been possible. Furthermore, acknowledgment is due to the following drug companies who assisted financially in bringing nationally recognized authorities to our conference: Ciba Geigy Corporation; Lederle Laboratories; McNeil Laboratories, Inc.; Merrell-National Laboratories; Pfizer Laboratories; Roche Laboratories; Sandoz, Inc.; Smith, Kline and French Laboratories; and E. R. Squibb & Sons, Inc.

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MMA ANNUAL MEETING MAY 17-18, ST. PAUL

May 16-17-18 are the dates for the 1979 MMA Annual Meeting. When your registration materials arrive, look for some interesting details.

If you attend the meeting on Wednesday, May 16, you can pick up CME course materials, attend the House of Delegates meeting and reference committees, enter the First Annual MMA Foot Race or the golf or tennis tournament. You can mingle with colleagues and exhibitors at the Annual Meeting Reception in the exhibit area, and enjoy a very special performance by The New Wizard Oil Troupe, an old-fashioned medicine show.

On Thursday May 17, the scientific program offers several courses listed separately elsewhere in this issue. Credits obtained at this program count toward the AMA Physician's Recognition Award, license requirements for the Minnesota State Board of Medical Examiners, Prescribed Credit for the Minnnesota Academy of Family Physicians, and the entire program is recommended as review material toward examination by the American Board of Family Practice. The faculty includes such notables as Dr. Joseph Pursch of California. His recent treatment of former First Lady Betty Ford brought national attention to the Alcohol Rehabilitation Service at Naval Regional Medical Center in Long Beach.

During the lunch break you're invited to dine with our featured speaker Dr. George Sheehan — cardiologist, author, running enthusiast, and medical consultant to "Physician & Sports Medicine" and "Running World" magazines.

In the evening a reception honors Doctor and Mrs. Robert Flom at the close of his term as MMA President. Among their guests are members of the MMA Fifty Club, Minnesota physicians who celebrate their fiftieth anniversary in the medical profession this year.

Friday May 18 includes another full schedule of CME courses, exhibits, House of Delegates and committee meetings, and specialty society meetings. Throughout the convention the MMA Auxiliary has activities planned especially for spouses.

Watch for registration materials in the mail this month, and in the March issue of MINNESOTA MEDICINE. We hope to see you in St. Paul.

S. V. Thorson M.D.
Chairman
MMA Subcommittee
on Scientific Assembly

Chlorpromazine's Entrance into Psychiatry

An Extremely Interesting Product

JUDITH P. SWAZEY, Ph.D.*

Chlorpromazine's synthesis and entrance into psychiatry exemplify the complex processes of scientific discovery and therapeutic innovation. CPZ's synthesis in 1950 grew out of nearly a century of researches in areas unrelated to the drug therapy of mental disease states. The discovery and testing of CPZ's use in psychiatry, in turn, also resulted from work in various research and clinical arenas, including surgery and the treatment of Parkinson's disease, as well as psychiatry. Many of CPZ's psychotropic successors have followed comparable paths of entry into psychiatry.

WE FREQUENTLY honor the birthdate or anniversary of great men and great ideas in the history of science and medicine, but it is relatively infrequently that we pause to pay tribute to a product of scientific and clinical research and discovery.

Thus, holding this symposium to commemorate the silver anniversary of chlorpromazine's (CPZ) entrance into psychiatry signals the fact that CPZ has proved to be far more than "an original product with extremely interesting properties in various therapeutic domains" — as it was characterized in a 1952 letter from Rhône-Poulenc to Mr. Francis Boyer, President of Smith, Kline and French.

CPZ, indeed, proved to be the first drug, in Western medicine, found to have specific psychotropic effects against a range of mental disease symptomatologies, particularly those associated with schizophrenia. The drug's entrance into psychiatry was a critical factor, if not the factor, in what many have viewed as a "revolution" in hospital psychiatry, opening up new avenues in the treatment and management of institutionalized patients and creating new needs and new options for the aftercare of those able to move out of the hospital and back into the community. In addition to its direct therapeutic impact, CPZ has had other, far-reaching effects through the pivotal role it has played in creating the modern scientific field of psychopharmacology, a field with a history that dates to antiquity.

Others have examined the impact of psychotropic drugs on basic and clinical research and on clinical practice over the past quarter-century. I'd like to turn back to pre-1952, to look at two quite separate events: how CPZ came to be, and how it entered psychiatry. It is a fascinating story, not only because of CPZ's importance, but because of the light it sheds on the complex processes of scientific discovery and therapeutic innovation — processes about which we still know relatively little, despite the political sound and fury that has engulfed them in recent years.

One might begin CPZ's history in 1950, when it was synthesized from a phenothiazine base by chemist Paul Charpentier in the laboratories of the Rhône-Poulenc Pharmaceutical Company, in Vitry-sur-Seine, France. Historically, however, CPZ represented an end-point as well as a beginning in the complex processes of scientific discovery and therapeutic innovation. The development of a drug for the treatment of mental disorders was not the central goal of the Rhône-Poulenc chemists and pharmacologists who formulated the research project that led to CPZ's synthesis. Rather, they were seeking to produce a phenothiazine derivative with a high degree of central nervous system activity, primarily for use as an anesthetic potentiator; a drug that would reduce the amount of anesthetic necessary for a given level of surgical anesthesia.

From the vantage point of retrospect, one finds that CPZ's synthesis in 1950 grew out of nearly a century of research in three major, intersecting areas, seemingly far removed from an unrelated to the drug therapy of mental diseases states. The first area began with the synthesis of phenothiazine in 1883 and the latter study of its possible uses, first as insecticides, veterinary anthelmintics, or anti-malarial drugs.

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Presented at the Symposium on 25 years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

The materials in this papter are drawn from the author's *"Chlorpromazine in Psychiatry. A Study of Therapeutic Innovation."* Cambridge, MA:MIT Press, 1974.

The second area was a series of investigations by pharmacologists, chemists, neurophysiologists, clinicians, and others that centered on the identification and study of histamine and then the search for antihistamines. Preeminent in this line of CPZ's history was Sir Henry Dale, whose decades — of work on histamine grew out of his interest in ergot alkaloids.

In 1944, the first phenothiazine amine compounds were synthesized, independently of work on the development of antihistamines. These two lines merged in 1946, when Rhône-Poulenc chemists found that one of the phenothiazine amines, fenethazine, possessed antihistaminic properties. Then, within a few months, Paul Charpentier synthesized a new phenothiazine amine derivative, promethazine, that proved to be a powerful antihistamine.

In 1946, laboratory and clinical investigators associated with Rhône-Poulenc also reported another new use for the phenothiazine amines, as highly effective antiparkinsonism drugs. In retrospect, with regard to the later discovery of CPZ's psychotropic effects, one of the most striking data in the first clinical report of diethazine as an antiparkinsonism drug is the statement that the patients' "psyches" seemed strongly influenced, with a "feeling of euphoria" replacing their "habitual depressive state."

Diethazine's effects on Parkinson's disease patients was one of several indications that the new phenothiazine amines might be exerting central nervous system effects of a hitherto unknown type. Another clue to their central nervous system effects lays in the discovery that the strong phenothiazine antihistamines, fenethazine and promethazine, commonly had a strong "sedative side-effect" in humans. Patients often reported feeling drowsy, dizzy, or "drunken" after taking these and other chemical-classes of antihistamines. Such sedative effects, however, had not been detected in pre-clinical tests with laboratory animals. Indeed, in high doses, the antihistamines often caused signs of pronounced excitation in laboratory animals.

Thus, another critical event for the development of CPZ came in 1947-1949, with the development of the first animal tests which could detect the central nervous system "sedative" effects of the phenothiazine amines (Ducrot at Rhône-Poulenc, and Winter at Merck) potentiation of barbiturates; (Macht at Johns Hopkins, and Winter — rat rope climbing [conditioned reflex] test).

The third major line of development that fed into the synthesis of CPZ was work on the nature and management of surgical shock. The central figure in this aspect of CPZ's history is a French surgeon, Henri Laborit, whose role has been, variously, ignored, minimized, or overstated. The controversy about Laborit's contributions to CPZ's development and entrance into psychiatry stems, I think, from two interrelated factors about the man and his work: the unorthodox nature of his theories about shock and methods for the management, and his aberrant career pattern within France's tightly structured scientific-medical system.

To combat the onset of shock in his surgical patients, Laborit developed a "pharmacological cocktail" of various agents, including antihistamines, to counter the effects of the chemical mediators that he believed acted on the autonomic nervous system to initiate shock. The principle antihistamine that Laborit began using in 1949 was promethazine, the phenothiazine amine derivative that Rhône-Pouleno had developed in 1946.

When he began using promethazine, Laborit recognized that the drug had what he termed three "infinitely precious" secondary properties: hypothermic, analgesic, and hypnogenic effects on his surgical patients. He began using promethazine for these secondary effects.

In a 1949 paper, Laborit drew a crucial distinction between the effects of morphine and promethazine on surgical patients. In contrast to morphine, he reported, promethazine causes a "euphoric quietude;" patients are calm and somnolent, in a state of repose and detachment. In producing this effect, he further stated, promethazine must be exerting some sort of central nervous system effect. Laborit's recognition of promethazine's relatively weak central action, as seen in the euphoric quietude it caused, represents a preview of *ataraxy*, a word coined in 1955 to describe the behavioral effects of chlorpromazine-like drugs.

Laborit's pharmacologic methods for managing shock, however unorthodox they were in terms of the prevailing views on the nature of the phenomenon and its treatment, thus led him to find two new uses for the phenothiazine antihistamine: as preanesthetic agents, because of their apparently central nervous system hypogenic and analgesic actions; and as agents for potentiated anesthesia, based on their hypometabolic effects.

By the fall of 1950, then, Pierre Koetschet and his colleagues at Rhône-Poulenc had a series of data indicating that the phenothiazine amine compounds already in use possessed a set of weak central nervous system properties which were independent of their antihistaminic effects. It was on this basis, in October

1950, that Koetschet drafted a research project, for the development of a new type of phenothiazine amine: one with maximally active central nervous system actions, irrespective of antihistaminic properties, that might find application as a preanesthetic agent or as a potentiator of anesthetics and similar agents.

Koetschet's project was implemented within a week, beginning with a screening of the various antihistaminic compounds already synthesized by Rhône-Poulenc. One compound, known as 3276 RP, was quickly found to have the highest central activity among their series of phenothiazine amines. This drug had been synthesized by Charpentier in 1944, and had remained on the shelf because it had proved to have the weakest antihistaminic activity among the series of phenothiazine amines that were prepared at that time. At the time that compound 3276's central activity was identified in the fall of 1950, Charpentier had just synthesized a new chlorophenothiazine compound, and decided to try branching the lateral chain of compound 3276 onto this new chlorophenothiazine diagram.

On December 11, 1950, Charpentier forwarded a small sample of the resulting compound, code-named 4560 RP, for pharmacologic testing. Preliminary tests showed that the new compound possessed exceptional central activity, and the decision was made to conduct a detailed study of the compound, which we know as chlorpromazine, as a prelude to clinical trials.

Then, on April 6, 1951, less than four months after it was synthesized, the therapeutic research division of Rhône-Poulenc received the first 18 samples of CPZ to distribute for clinical testing. As Koetschet told the author in 1972, the institution of clinical trials with a new drug like CPZ was "much easier, much less formal, in 1951 than today. We had no clear idea of what CPZ would do in man. We had the strong impression that it was an interesting, non-toxic drug, that would be very useful once the best areas of its use were discovered through clinical tests."

Although Rhône-Poulenc did not initially plan psychiatric trials with CPZ, they were alerted to any clinical data suggesting that their new product might have applications in psychiatry. Rhône-Poulenc, for example, knew of the prior sporadic uses of synthetic antihistamines, such as phenbenzamine and promethazine, by psychiatrists for their sedative effects on patients, and of Laborit's use of promethazine for the "euphoric quietude" it produced in surgical patients. The company's data on CPZ's effects on conditioned reflex behavior in laboratory animals, showing that CPZ abolished conditioned reflex behavior in rats, also pointed to the drug's behavioral effects. Rhône-Poulenc's first clinical indication that CPZ would prove useful in psychiatry came on April 10, 1951, in the drug's first clinical test, when a Dr. Schneider found that CPZ + barbiturates calmed a manic patient, whereas barbiturates alone had no effect. The use of CPZ to potentiate barbiturates was one of the three principal ways in which the drug was first tried by psychiatrists. The second way, also evolving from its known potentiating properties, was for sleep therapy: a procedure in which patients were maintained, for days or weeks, in long periods of unconsciousness; a popular form of therapy in Europe at the time. The third therapeutic modality, one which represented a marked departure from the major thrust of CPZ's development as a potentiator, was the prolonged and continuous administration of CPZ alone.

After Schneider's single trial with CPZ on a manic patient — which led Rhône-Poulenc to list "interruption of manic crises" among the potential uses for CPZ in a December 1951 "Provisional Note" — the drug's second point of entry into psychiatry came in December 1951. Sigwald and Bouttier, who had conducted the clinical trials with one of CPZ's predecessors, diethazine, for Parkinson's disease, began testing CPZ as an antiparkinsonism drug in April 1951. While CPZ did not prove effective in this area, Sigwald and Bouttier's observations of its behavorial effects with certain of their patients led them to begin a series of trials in December 1951 with psychotic and neurotic patients, using both CPZ alone and CPZ + barbiturates. They were thus the first to employ CPZ alone, soon the dominant form of CPZ's use in psychiatry. Their extensive case reports' paper, however, was not published until 1953, and the credit for establishing the use of CPZ alone rightly has gone to two other French investigators, psychiatrists Jean Delay and Pierre Deniker.

The first oral report, and subsequent published paper, on CPZ's use in psychiatry was made in 1952, by a group of psychiatrists from the Val-de-Grâce military hospital in Paris, where Henri Laborit worked.

At Laborit's urging, based on his use of CPZ for "artificial hibernation" in surgical patients, Hamon et al. administered CPZ + barbiturates for 20 days to a 24-year-old psychotic patient, who then was discharged as "adaptable to a normal life."

In the spring of 1952, through knowledge of Hamon's work, Laborit's use of the drug and Sigwald and Bouttier's trials, a number of investigators began using CPZ for sleep therapy. The most critical event for CPZ's entrance into psychiatry, however, occurred in March 1952, when Jean Delay and Pierre Deniker began their first trials with CPZ, administered alone, at St. Anne's Hospital in Paris. By July 1952, they had demonstrated CPZ's unique "tranquilizing" effects on a range of psychotic behavior in 38 patients. Delay and Deniker's work, as well as that of Laborit and the other French psychiatrists who first tested the new drug, gradually led Rhône-Poulenc to reassess their initial views of the drug's primary uses, as a potentiator and to prevent nausea, and to place as great or greater emphasis on its uses in the field of neuropsychiatry.

Thus, as CPZ "migrated" from France to other countries around the world, it was received and tested largely, but not solely, in terms of its possible applications in psychiatry. CPZ began its journey to the U.S. in April 1952, when Rhône-Poulenc, foreseeing difficulties in attempting to market the drug in this country, contacted SK&F to inquire about a possible licensing agreement. Rhône-Poulenc had previously approached two other American firms, but neither was interested in the new potentiator. A pharmacologist who worked for one of those companies in 1952 remembers, with chagrin, that his firm turned down the opportunity to acquire CPZ because "the management didn't want to gamble on a new drug that had no clear-cut marketing areas with large sales potential." Francis Boyer's response to Rhône-Poulenc's offer, however, was prompt and affirmative: "The compound is exceedingly interesting at first glance," he replied on April 15, 1952, "and I wonder if you could arrange to send us, as soon as possible, 500 grams of the pure substance for our use in tests here."

Initially interested in CPZ as a potentiator, SK&F soon seized on the new drug's possible uses alone. "At the moment," the company's Director of Development wrote in May 1952, "I believe that the emphasis on the use of the compound for its inherent properties in neurologic and psychiatric problems presents the most promising prospects for development."

Two years later, in May 1954, after extensive laboratory and clinical testing, SK&F began to market CPZ as Thorazine. Within 8 months, the drug had been given to an estimated two million patients.

In a long paper of 1953, Jean Delay reviewed the various methods of and results with CPZ therapy that psychotherapeutic ideology among psychiatrists, an one-half. In his paper, foreshadowing the flood of reports that would come from hospital psychiatrists in the U.S. and other countries around the world in the next few years, he spoke of how the use of CPZ had "revolutionized" the atmosphere of the disturbed wards in Paris' mental hospitals. Like most revolutionaries, however, CPZ's arrival on the psychiatric scene in the U.S., as in France and other countries, was met with something less than ardor in many quarters, for a number of reasons. In the U.S., for example, CPZ's introduction took place within a predominantly psychotherapeutic ideology among psychiatrists, an orientation not geared to the acceptance of a drug therapy approach to mental disorders. Even among psychiatrists disposed to try drug treatments, CPZ was viewed, initially, as just a "glorified sedative," another in a long procession of drugs that psychiatrists had tried, with little success. CPZ, as I noted, was first used in psychiatry for the treatment of mania and other forms of agitation, and thus was introduced the still-used word "tranquilizer" to describe its effects on mood and behavior. The definition of CPZ's fuller role in psychiatric therapy, as not just a tranquilizer but as an antischizophrenic drug, an agent with highly specific effects against a range of schizophrenic symptoms, emerged gradually through the 1950s, with the development of new methodologies for evaluating the clinical efficacy of psychopharmacological drugs. It was not until the NIMH collaborative study of phenothiazine treatment in acute schizophrenia, conducted in 1961, that we gained definitive evidence that CPZ, first developed as a potentiator for other drugs, was in fact a highly effective antischizophrenic agent in its own right.

This, then, in a thumbnail sketch, is the story of CPZ's origins and its entry into psychiatry, a story that spans many decades and many diverse fields of research and clinical practice. In reflecting on the growth of psychopharmacology and the proliferation of psychotropic drugs since CPZ, one is struck by how similar the pattern of innovation has been. The great majority of new drugs have continued to come from pharmaceutical companies, whose research efforts are premised on varied types of prior developments of the sort that underlay CPZ's synthesis. Many other early psychotropic drugs, like reserpine and iproniazid, entered psychiatry much like CPZ did, after their effects on mood and behavior were observed in connection with therapeutic use for non-psychiatric conditions. Other compounds, such as the new phenothiazines modeled on CPZ, were developed by lengthy empirical screening procedures to identify the few among thousands of possible compounds both safe and efficacious enough to move from the laboratory to the clinic. Psychopharmacologists today know far more clearly than was possible when CPZ appeared the types of effects they would like a drug to exert. But in pharmacology generally, as Louis Lasagna has commented, the state of the art has not yet permitted the "luxury" of "thoroughly rational drug development."

The drug therapy of mental disease states and the disciplines of basic and clinical psychopharmacology of which it is now a part have grown enormously in both scope and sophistication over the past quarter century, since CPZ appeared. The history of CPZ, however, can still inform those who would better understand the present as well as the past nature of therapeutic innovation in these fields.

Continuing Medical Education

Q and A — CME

Question: What is the position of the Minnesota State Board of Medical Examiners regarding the acceptance of credits obtained by physicians attending C.M.E. courses outside of Minnesota?

Answer: Meetings sponsored by one of the National Medical/Osteopathic Organizations, a State Medical/Osteopathic Organization, or a recognized national sub-specialty organization are automatically Category I.

If the material has been recognized by the L.C.C.M.E. or the A.M.A. it will be accepted as Category I.

Any meeting sponsored or cosponsored by a United States or Canadian Medical School is recognized as Category I.

If a program does not satisfy one of the above standards the material can be sent to the State Board with the curriculum vitae of the individuals giving the course and the program of the course. The category will be determined individually by the Board for the specific course.

Question: What is regarded as the official date for the Board Certification, the date of examination or the date of notification of passing, eg exam taken in October, notification in February?

Answer: The Board has agreed that it would be wise to accept the date that notification was received of passing the exam.

Please direct all inquiries to the Minnesota State Board of Medical Examiners.

Questions from Minnesota Physicians Concerning Continuing Medical Education may be Addressed to:

J. C. Cain, M.D.
Suite 900
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Those answered in MINNESOTA MEDICINE are the most common or the most appropriate to a specific time. Queries from individuals will be answered as rapidly as possible only if a self-addressed stamped envelope is enclosed.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
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OVERDOSAGE: Manifestations of acute overdosage include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Overdose of pharmacologically similar compounds has resulted in fatal poisoning, usually terminating in convulsions and coma. Management of acute Tenuate intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Intravenous phentolamine (Regitine®) has been suggested on pharmacologic grounds for possible acute, severe hypertension, if this complicates Tenuate overdosage.

Product Information as of April, 1976

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References: **1.** Citations available on request — Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. **2.** Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M. A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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For prescribing information see opposite page.

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*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

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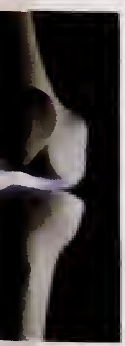
RHEUMATOLOG



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Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
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Psychopharmacology and Family Practice

HARLEY RACER, M.D.*

In 1952, as chlorpromazine was introduced into clinical practice, half of the medical school graduates in Minnesota entered general practice. Attrition was severe, and *Family Practice* developed to fill the need. Eighty medications were listed in 1956 as treatment for "emotional instability." During this period, treatment of mental illness shifted from long-term institutionalization to outpatient and/or community hospitalizations. These three historical trends have meshed to change the impact of modern psychopharmacology on family practice. Today family practitioners call on expert consultants to assist treatment, as well as refine their prescribing habits through continuing education. The 93 psychopharmacological agents listed in the Physicians' Desk Reference today are classified into 13 subcategories for rational selection.

The evolution of family practice from "general" to "family" and "community" practice places the family practitioner in the position of assuming more responsibility for recognizing and managing significant mental and emotional disorders.

TWENTY-FIVE YEARS ago, as the age of modern psychopharmacology was begun by the introduction of chlorpromazine (Thorazine) into clinical use in 1952, general practice was the portal of entry into clinical life for about half of the medical school graduates that year from the University of Minnesota. General practice was typically characterized by limited preparation (usually one year of rotating internship), and by a lifetime of uncontrolled overwork — an unceasing series of episodes of illness, injury, birth and death — rarely comprehended as a sensible, interrelated whole. The reward was all too frequently personal disaster for the physician, his wife, children, and his patients. Attrition from the ranks of general practitioners was steady and understandably high. Less than one in five of that 1952 class remained in general practice in the cities and towns of Minnesota 20 years later.

Family practice emerged over that 20-year-period, as older and younger general practitioners together developed a new discipline: the personal physician giving care to patients that is integrated, holistic, continuous, and that comprehends the intrapersonal, family and community factors that are involved in being well and being ill. Family practice demands constant self-knowledge by the physician, including commitment to the best principles of basic and applied clinical science, in caring for patients.

It is in this frame of historical reference that the family physician has been challenged by the rapid development of the field of psychopharmacology over these 25 years, moving from pill-pusher (pink for A, blue for B, etc.) to rational prescriber of potent chemicals while at the same time taking on the habits and styles of a young and developing discipline of practice. Psychiatry was changing as rapidly. Many family physicians-to-be had their first exposures to serious psychiatric disorders in the dispensaries and military hospitals of World War II. There they learned that the place for serious psychiatric problems was in the mysterious and remote institutional settings of the psychiatry wards. Undergraduate experience just before the 1952 introduction of phenothiazines reinforced the attitude that psychiatric illness was something the family doctor would triage and refer as quickly as possible. Those who were preparing for general practice did not really expect to be caring for many patients with serious mental and emotional illness.

A Period of Wonder: The 1950s.

With the introduction of phenothiazines in 1952, the chemical revolution of management of serious psychiatric illness began to return patients to the family and the community, and thus into the practice of the family physician. These patients had previously been destined for life in mental institutions. Family doctors began to experience the difference in their practice lives, needing now to know about the new agents, their efficacy, limitations, and complications. Table 1

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Presented at the Symposium on 25 Years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

TABLE 1

Average Daily Census Minnesota State Mental Hospitals		Minnesota Total Population	Ratios
1950		2,982,483	
1955	11,300		1:265 (377/100M)
1960	10,200	3,413,864	1:350 (285/100M)
1965	6,700		1:544 183/100M
1970	3,200	3,805,069	1:1190 84/100M
1975	1,700		1:2350 42/100M

Minnesota Department of Public Welfare Informational Brochure 1977.
U.S. Census

shows what happened in mental hospitals in Minnesota.

If chemicals could change the management of so mystifying and frightening a disorder as schizophrenia, who knew what might become possible? Sulfa and penicillin had appeared in the venereal disease and trauma wards of World War II and had changed the world of practice in those problem areas. Family physicians began to adapt to major changes in the goals and possibilities for management of emotional and mental disorders.

A Period of Credulity: The 1960s.

By 1956, only chlorpromazine (Thorazine) and meprobamate (Equanil) had joined the rauwolfias in the Physicians' Desk Reference.[2] The Tenth Edition, already a frequently-used guide for prescribing by general practitioners, listed no category such as "Tranquilizers," or "Antidepressants," but rather clumped the new agents under the title "Emotional Instability." There were 80 entries under that heading, and family physicians were eager to provide relief for symptoms of anxiety, insomnia, fatigue, depression, while patients increasingly expected such relief by chemicals prescribed for them by their family doctor. So it was that many family physicians became unwitting enablers of their patients' search for peace through chemical prescription.[3]

It was during this period, that family doctors began to accept more responsibility for patients with major emotional and mental disorders. Patients were being treated in community hospitals over weeks instead of months or lifetimes. Family doctors began to participate more and more in the continuing care of their patients, following them through in-hospital care just as the family doctor would follow patients through the course of surgical and medical illness, working with and learning from the specialty consultant. So family doctors began to learn more about the impact of psychiatric illness on patients and families.

While family doctors thus came into contact with the new drugs, they learned effective ways to use them from their consultants. The increased impact of mental illnesses themselves in the family physicians' practice stimulated awareness that the family physician would need to know more about the relationship of family function and dysfunction and of community factors both in the etiology and treatment of these illnesses.[4] So interest and the beginning of clinical research into family and community factors, in illness and health, became fundamental to the change from "general" to "family" practice.

Meanwhile, family doctors and their consultants went on prescribing both old and new chemicals, not always with precision, and sometimes with more reliance on the drugs than was warranted (Table 2).

For too many patients in this period, prescribing by family doctors was not as critical, not as discriminating, not as soundly based on accurate diagnosis and on basic psychopharmacologic principles as it might have been even then — and as it must be now. The reference case outline characterizes many of these problems: overuse of drugs, polypharmacy, inaccurately chosen agents, and inappropriate dosages.[6,7]

A Period of Challenge

The thalidomide disaster became apparent in late 1962, and its alarum awakened many general practitioners to examine more carefully drugs they were prescribing for their pregnant patients. But more careful prescribing, based on teratogenicity, did not inform the general practitioner prescribing for all of his patients, until other factors began to have their effect in the development of the family physician of today.

TABLE 2
Case Report

FEMALE, b. 1916
eldest daughter. two brothers. one sister.
mother: chronic invalid (wheelchair)
father: stern and distant

Problem	"Other" Drugs		Psychotropic Drugs
1926 Problem #1 Migraine age 10			
1936-1947 College graduate school psychiatric social work			
1948 Problem #1 Migraine Psychotherapy 1 year			
1950 Married age 34, adopted two pre-teen daughters			
1958 Problem #1 Migraine	ergot phenobarbital belladonna dilantin		Librium "other tranquilizers"
Problem #2 Thyrotoxicosis '131 hypothyroid	synthroid		
1961 Problem #1 Migraine neurological evaluation pneumoencephalogram "retrogressive" ECT demerol addiction ergot induced peripheral neuritis			Sparine 800mg/day
1961-1963 Problem #1 Migraine psychotherapy 2x/wk ($60) "free of headaches" 1962	fiorinal demerol	Compazine	Sparine ($30/mo) 800mg/day
1966 Problem #1 Migraine 4-vessel arch study	fiorinal demerol	Compazine	Sparine 800/mg/day
1969 Problem #3 Myocardial Infarction anticoagulation (large doses) gastrointestinal bleed	fiorinal		Sparine 800mg/day
Problem #1 Mirgraine	demerol	Compazine	
1970 Problem #1 Migraine hypnotism	propanolol fiorinal demerol	Compazine	Sparine 800mg/day
1971 Problem #4 Depression personal physical conditioning relaxation training		Compazine	Sparine 800mg/day Vivactil 5mg/day
Problem #1 Migraine	fiorinal dilantin sansert		
1972 Problem #1 Migraine biofeedback training	fiorinal dilantin	Compazine	
Problem #1 b hematuria IVP, cystoscopy			
Problem #1 c demerol addiction withdrawal			

(Continued)

TABLE 2 (Continued)

1972	**Problem #4 Depression psychotherapy**		**Sinequan 100mg/day**
	Problem #1 Migraine	**dilantin**	
	Problem #5 Menopausal Syndrome (vasomotor instability)	**premarin**	
1973	**Problem #4 Depression psychotherapy**	**emesert**	**Sinequan 100mg/day**
	including day hospital	**talwin**	**Sinequan 100mg/day**
	Problem #1 Migraine 6 weeks without medications except	**dalmane**	
	Problem #1 Migraine no medications September, October, November		
1974	**Problem #1 Migraine**	**fiorinal**	**Sinequan 100mg/day**
	Problem #4 Depression		
	hospitalized, withdrew meds	**(talwin)**	**Sinequan 100mg/day**
	resumed psychotherapy	**(fiorinal)**	
1975	**Problem #1 Migraine**		
	Problem #4 Depression counseling	**None**	**None**

By the mid-1960s, some general practitioners among the survivors of general practice, began to conceptualize and to promote an entirely fresh approach to being the primary physician, other than the life of the general practitioner — hectic, disconnected, episodic care in volumes seeming endless — a life of reaction to a world full of illnesses and injuries. Family practice was developed with a fundamentally different commitment by the physician to himself and to patients and families. The new commitment encompassed self-knowledge, comprehension of sources of illness within the person, the family, and the community, continuity of care for lifetimes, and continuous engagement of doctor and patient in seeking health and prevention of illness.

Into that kind of ferment came the challenge for more responsible, comprehensive care of patients with mental and emotional disorders and with that, the demand for more discriminating use of psychotropic medications. The attempt to discover this kind of meaning in the new specialty has emphasized continuing education as a characteristic of the family physician, and has increased the demand that the family physician be first of all knowledgeable in the basic and applied clinical sciences, which are the ground on which primary physicians stand in caring for and caring about people. Integration of biological and behavioral aspects of patient care is the hallmark of the new specialty.

A Period of Discrimination

The history of psychopharmacologic prescribing by general practitioners has not always been satisfying. Both European and American observers reported steady increases in the amounts of psychotropic drug prescribing by general practitioners between 1950 and 1975. Paris points out that, in 1973 although the number of patient visits to general and family physicians had remained fairly constant between 1961 and 1973, the percentage of all prescriptions for psychotropic medication had risen from 3% to 42%. Similar reports appear in the American literature. But there are indications that family physicians of the new breed (including converted general practitioners) are attempting to care for their patients more nearly holistically.[8-11]

There is evidence that the family physician is continuing to examine and evaluate what he is doing and what he might be doing better. He is assuming more responsibility for the recognition and management of significant mental and emotional disorders.[12] One of the earliest reports of the content of general practice in American literature was that of Connolly, Malerich, and Wegletiner[13] in 1969 which identified "psychiatric" visits as less than 1% of their total, and in the seventeenth rank of frequency in their practice. In the massive study of content of family practice reported by Marsland and others in Virginia in 1976,[14] more than 5% of all visits to family doctors were coded in the diagnostic category of ''mental and behavioral'' problems, and recognized anxiety and depression were reported with frequencies that would rank 5th among visits to family physicians.

Family physicians are also becoming more exacting and more discriminating in their prescribing of psychotropic drugs. In a study of eight family practices in the Philadelphia area in 1975, Hesbacher[15] concluded that family doctors are ''choosing from a limited range of . . . medications . . . regarded as most effective, and are judicious in the choice of patients for whom pharmacotherapy is prescribed.''

Returning to the reference case in Table 2, it can be seen that in the past five years, the patient experienced a reduction in the amount of drugs prescribed, compared with the previous ten years, and has been more accurately diagnosed, benefitting by more appropriate overall therapy.

The 1977 Physicians' Desk Reference[16] now lists 93 potent psychopharmacologic agents available for prescribing by family doctors, divided into more than 13 classifications. Thus the family doctor must continue to be taught throughout his practice life by basic scientists and clinicians learned in psychopharmacology.

The practical questions for the daily life of the family physicians will continue: Which patients can be benefitted by a psychopharmacologic drug? In what specific ways? By which specific chemical(s)? In what dosages? For what optimum periods of time? With what known side effects? With what cumulative injury? At what dollar cost?

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Physicians Warned to Keep Prescription Pads in a Controlled Area

The Minnesota Board of Medical Examiners is strongly urging physicians to take special precautions to keep prescription pads in controlled areas where patients cannot pick them up.

The Board advises that a large number of addicts are entering doctor's offices, picking up prescription pads, keys, and even rolls of stamps while there as patients. They then forge prescriptions to obtain drugs, the most popular being Dilaudid and Percodan. Visits are made to several doctors for the same complaint and prescribed drugs are then sold on the street.

Two of the ruses that are being used to get legitimate prescriptions from doctors are pain as a result of tooth loss, or pain from a bad back. Law enforcement authorities in the metropolitan area are aware of a person passing himself off as a Dr. Walker to hospital personnel, and telling them he is expecting some calls. His cohorts go to a drug store with a forged prescription and suggest the druggist call Dr. Walker for confirmation. The current rash of prescription pad thefts and forgeries may be due primarily to the shortage of Heroin on the street.

Minnesota Medical Association
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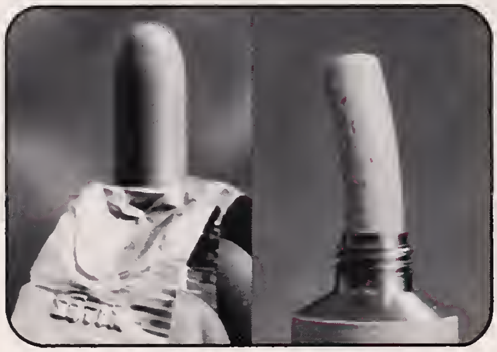
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Each gram of Anusol-HC Cream contains hydrocortisone acetate, 5 0 mg, bismuth subgallate, 22 5 mg, bismuth resorcin compound, 17 5 mg, benzyl benzoate, 12 0 mg, Peruvian balsam, 18 0 mg, zinc oxide, 110 0 mg, also contains the following inactive ingredients, propylene glycol, bismuth subiodide, propylparaben, methylparaben, polysorbate 60 and sorbitan monostearate in a water-miscible base of mineral oil, glyceryl stearate and water

Indications: Anusol-HC Suppositories and Anusol-HC Cream are adjunctive therapy for the symptomatic relief of pain and discomfort in external and internal hemorrhoids, proctitis, papillitis, cryptitis, anal fissures, incomplete fistulas and relief of local pain and discomfort following anorectal surgery

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Precautions: Symptomatic relief should not delay definitive diagnoses or treatment If irritation develops, Anusol-HC Suppositories and Anusol-HC Cream should be discontinued and appropriate therapy instituted

In the presence of an infection the use of an appropriate antifungal or antibacterial agent should be instituted If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled

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Anusol-HC is not for ophthalmic use

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Anusol-HC Cream—Adults After gentle bathing and drying of the anal area, remove tube cap and apply to the exterior surface and gently rub in. For internal use, attach the plastic applicator and insert into the anus by applying gentle continuous pressure Then squeeze the tube to deliver medication. Cream should be applied 3 or 4 times a day for 3 to 6 days until inflammation subsides Then maintain patient comfort with regular Anusol Ointment

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Impact of Depot Neuroleptics on Psychiatry

LIONEL CORBETT, M.D.*

The advent of phenothiazines revolutionized the management of Schizophrenia, and maintenance therapy with these compounds often prevents relapse. The use of depot neuroleptics reduces the rate of drug defaulting and further helps to maintain such patients in the community. The depot preparation is also valuable when failure to absorb oral medication occurs, and offers the additional advantages of economy, improved morale and reduced total drug dosage. Unfortunately, community resources are often inadequate for the full advantage of the drug effects to be realized. Some physicians are still not titrating individualized dose regimens or using high enough doses in refractory patients, whereas some patients are being over treated. Depot butyrophenones and thioxanthenes are also becoming available, thus greatly extending the range of applicability of this modality.

EACH NEW ADVANCE in medicine brings with it both new advantages and an attendant set of new problems, previously unforeseen. The advent of depot neuroleptics is no exception.

Before the advent of the phenothiazines in the 1950s, the treatment of schizophrenia was a relatively thankless task. Occasional remissions occurred, sometimes apparently related to electroconvulsive therapy or deep insulin therapy. These were usually of short duration. A diagnosis of true schizophrenia carried with it the prospect of chronicity, and often little more than the likelihood of long time custodial care. The phenothiazines enormously changed the acute manifestations of the illness. As a result hospital organizations and ward atmosphere could be markedly improved.[4] A new era was rightfully heralded. A marked fall occurred in the in-patient mental hospital population. The doors of some wards could be opened. The length of stay after acute illnesses was shortened,[23] and the hope of a community mental health system began. For a time it seemed possible that traditional mental hospitals would become obsolete. However, although the total number of in-patients fell, the re-admission rate increased, and a small group of intractably ill people could not be discharged. Notwithstanding, ward conditions for such patients improved, and it was clear some out-patients were being kept out of hospitals because of neuroleptic therapy. Accordingly, interest grew in maintenance therapy because it was quite rigorously demonstrated to prevent relapse.[8] Various difficulties of maintenance therapy emerged.

First, the large number of discharged patients greatly overtaxed community resources available to care for them. It is now obvious such patients cannot be self-sufficient without permanent community help. To achieve good adjustment, social support must be added to medication regimes which are not adequate alone.[14] The level of community disturbance caused by discharged schizophrenics is very high. Brown (1963)[5] followed 156 long-stay patients and showed that 56% caused distress to relatives, and in 25% of these cases this was severe. Half of a group of short-stay patients deteriorated within two weeks of discharge, of which two-thirds were re-admitted. Goldberg (1967)[11] showed that out of 75 male patients discharged from hospital, 38 of their families needed help. Because of inadequate community resources, great stress was often placed on families. While community mental health clinics are increasing in number, the social cost is considerable (Arnhof, 1975). Parenthetically, it should be noted that many female schizophrenics maintained in the community are having babies.

Second, large numbers of out-patients relapsed because they discontinued their medications, and most of these need to be re-admitted.[22,24] Further, 19% of in-patients do not take their tablets.[12] Many patients did not relapse for weeks or months after stopping treatment — they felt uncomfortable because of side-effects and were generally unconvinced that they benefited from medication. Others refused because of mistrust, some simply were too apathetic or disorganized to comply and for some expense or the availability of a physician were problems.

Third, it has become clear that neuroleptics do not cure the illness, nor do they manage it in the sense that insulin helps diabetics. They certainly alter its course

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and prevent its florid manifestations, but do not prevent the personality changes, affective blunting and loss of volition which characterize the malignant or process schizophrenia. In spite of the large number of compounds available, these comments apply uniformly. Not only are the primary handicaps of schizophrenia a problem, but the secondary handicaps of any chronic illness intrude, namely attitudes of apathy, resentment, and low self-esteem developed by the patient and the family, which lead to added social incapacity and mitigate against rehabilitation.[28]

A fourth drawback is highlighted by the problem of tardive dyskinesia. This complication makes it essential that we only prescribe long-term maintenance neuroleptics to those schizophrenics who really need it. It is not yet completely clear how to identify this group among acutely presenting patients during their first illness. At the other end of the time scale, Prien et al. (1972) have shown that after 15 years of hospitalization only 15% of schizophrenics relapse when medication is discontinued, although 50% of those ill for a shorter time relapse. Clearly, many patients are receiving unnecessary therapy.

Above all, care must be taken, to separate out atypical affective disorders from schizophrenia. Too many treatment-resistant schizophrenics are incorrectly diagnosed as many are manic-depressives.

Fifth, the education of some trainee psychiatrists in psychoanalytically oriented schools leaves them totally inequipped to take care of long-term patients with depot neuroleptics. In some such institutes, pharmacotherapy is still looked down upon as a second rate modality and is badly taught.

Sixth, it is still difficult to obtain adequate health insurance for outpatient psychiatric care, probably due to feelings that mental illness is life long, intractably hard to treat, and perhaps due to suspicions about the variety of treatments offered for the same illnesses.

Depot Neuroleptics

This then is the climate in which depot neuroleptics (DN) were introduced. They offer the following advantages:

1. Greatly reduced relapse rate compared with oral maintenance therapy.[7,10,13] Even on DN however, drug defaulting still occurs — up to 18% in Johnson's series[15] largely because of refusal to have injections or drift away from supervision.
2. Problems of malabsorption from the gut[1] and premature deactivation in the liver are by-passed, permitting reduced total drug dosage. Often patients refractory to oral medication respond well to DN.
3. Absence of over-sedation and autonomic discomfort found with weak phenothiazines.
4. Economy of nursing time and money spent on medication.
5. Improved patient and family morale, because of an absence of daily pill taking and obviously reduced relapse rate leading to some hope for the future.
6. Patients who require maintenance therapy but do not reliably take it can be kept in the community using DN.
7. Early relapse treated with DN can prevent the need for rehospitalization with substantial saving in human and economic terms.
8. Failure to respond to depot phenothiazine indicates true unresponsiveness of the illness to phenothiazine and clearly points to the need for a different class of agent. There is no doubt as to whether the patient took or absorbed the medication. By contrast, failure to respond to an oral neuroleptic, even if one is certain that it is being taken, always leads to doubts about absorption or the question of rapid metabolism.
9. Clinics dispensing DN can be run by psychiatric nurses rather than physicians. In Birmingham, England, a decanoate clinic was run by four nurses together with home visits if necessary. Only 8.7% of attenders are unreliable. The nurses liaise with the GP and psychiatrists as necessary, and the patients automatically receive 6 monthly psychiatric reviews. This group reports only a 5% one year relapse rate, compared to the usual 50% rate on oral medications.[21] This is one answer to the shortage of psychiatrists in some areas.
10. Depot fluphenazine is a safe drug. There are no known adverse interactions. The only important side effects are strio-pallidal, which are usually manageable. There is evidence that DN are safer than many oral neuroleptics since there have been no reports of DN related jaundice, blood dyscrasias, hepatotoxicity, ocular or skin damage, although these are well-known side effects of chlorpromazine and thioridazine. Seizures are almost unknown and autonomic changes are minor compared to those produced by weak phenothiazines. In spite of this, one still hears the criticism that the drug is dangerous because "once given it cannot be removed" — ignoring the well established fact that after loading with oral phenothiazines they too cannot be cleared for several months. It has been suggested that depressions may be caused by depot fluphenazine, although this is disputed because of the known proclivity of untreated schizophrenics towards depression. In any case, flupenthixol decanoate is most valuable for maintenance treatment of patients prone to this complication.[16,17]
11. Because of the low total drug dosage used in DN maintenance, the risk of developing tardive dyskinesia may be reduced in some patients.
12. Because of the advantages of safety, certainty of absorption, speed and duration of action and reduced total drug dosage, DN have often been used in the treatment of acute manic and schizophrenic psychoses.[6]
13. The advent of DN of different chemical classes to the phenothiazines, namely fluspiriline and flupenthixol, widens their applicability.

Problems of Depot Neuroleptics

The advantages outlined highlight the need to link medical advances with social change for their full benefits to be realized. The advent of DN have illuminated the public health aspects of schizophrenia. In the USA, in 1969, there were 180,000 resident schizophrenics in mental hospitals. This is 15,000 less than the 1968 figure and a 30% decrease since 1962.[20] Clearly, growing numbers of patients are treated as outpatients. If community services are inadequate, they drift aimlessly and appear frequently in court, oscillating from jail to hospital.[26] They also become ill with malnutrition and tuberculosis. The mental health of relatives may suffer under this chronic stress, many of them trying hard to maintain a turbulent and very trying person in the house. There is an obvious disparity between the advantage of DN and current resources for patients who are maintained on them. It seems that maintenance neuroleptics allow the schizophrenic to be relatively insulated from and hence to tolerate a greater degree of social stimulation. This can only be valuable if rehabilitation services of the kind described by Affleck[2] (1975) are available.

Paradoxically, a further potential drawback is provided by patients who do in fact attend regularly and monotonously for injections, and make no demands. The risk is that no one will attempt to reduce the dose or frequency of their injections. These goals are often both possible and desirable with long-term patients. They become routine cases, handed from therapist to therapist over time. It is essential to tailor the dose of DN to the individual patient. There is no such thing as a standardized dose regimen although in the majority of clinics DN are prescribed in a stereotyped manner. Johnson (1975)[16,17] has estimated that nearly 50% of cases are being over-treated because of this. In my practice the range has been typically from ½ cc every six weeks to 4 cc per week for maintenance, with all manner of combinations of doses and intervals between these limits. There are reports of doses of 5 cc and 10 cc of fluphenazine decanoate per week given to chronic patients with no toxic effects on the eye or heart.[18,27]

There may also be a tendency to forget to attempt to discontinue or at least reduce antiparkinsonian agents, which is nearly always possible. When patients relapse, especially if one has never seen them acutely ill but is relying on the history of another facility, one must always re-establish the diagnosis and never accept a "label" which may be wrong.

Problem of Treatment Dropouts

It is important to recognize that treatment dropouts occur in other fields of medicine. A review of the general medical literature suggests that 15-90% of medical patients do not comply with doctor's orders[9,19] This is especially well-known in relation to the treatment of tuberculosis and hypertension. There are many parallels with the non-compliance of schizophrenic patients. Lower socio-economic groups and those without supportive families are the least likely to comply in both cases, although there are no good predictors of compliance. Compliance decreases over time with any long illness, and complex treatment regimens are followed less well than simple regimens. Errors in dose and timing of medication are also common among medical patients.[3] The use of a depot preparation gives us a distinct advantage over our medical colleagues because of its simplicity and controllability.

Finally, I would stress the importance of:

1. Firmly installing the patient in the sick role by explaining that he has a well-known illness for which we have a helpful therapy, that he and his family are not to blame for becoming ill, and his cooperation is important. This simple step is often omitted.
2. Where possible, educate the patient and family about the nature of the illness, the nature and purpose of the injections, and the possible side effects and how to deal with them.

These measures enhance the overall efficacy of DN treatment of schizophrenia and improve compliance.

Legal Aspects

A Minnesota probate court in a recent decision* placed DN in the same category as ECT and psychosurgery as "intrusive forms of psychiatric treatment which requires the consent of the patient." They found the patient in this case competent to refuse treatment and that the physician failed to show the use of decanoate to be reasonable and necessary. This patient had had three admissions, successfully treated with oral phenothiazines, but refused to take medication. The court said that the physicians could have administered the decanoate when she was ill, but not now that she was recovered. The court said that the doctors had failed to explore using psychotherapy. They also noted that DN could only be used against the patient's consent if the patient is acutely psychotic.

The failure to grasp the nature of schizophrenic illness is evident in these comments. Later the Minnesota Supreme Court ruled that DN does not qualify as intrusive therapy. This ruling concerned a young paranoid schizophrenic who refused to cooperate in treatment.† This kind of legal scrutiny is typical of the warning given by Robitscher, who wrote of the danger that legal policy will determine the structure of American Psychiatry, and that the psychiatrist will then be taken away from patient care and forced to spend time in litigation and the practice of defensive psychiatry.[25] This is certain to discourage physicians from trying high doses and unusual regimens in treatment-resistant cases of schizophrenia and depression, and will encourage conformity and entrenched rigid forms of practice.

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*(Psychiatric News, April 15, 1977.)

†(Psychiatric News, May 20, 1977.)

Lawyers tend to accept what is current practice as being correct, even though it often can be shown that this leads to suboptimal treatment for many patients. The use of DN is such a major advance that this must not be allowed to happen.

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Parkinson's Disease, Huntington's Disease and Tardive Dyskinesia

Neurochemical Pathology and Treatment

EDUARDO S. TOLOSA, M.D.*

The neurochemical pathology and pharmacology of two naturally occurring disorders of the basal ganglia, Parkinson's disease and Huntington's disease, and of the neuroleptic induced extrapyramidal syndrome tardive dyskinesia are reviewed. In Parkinson's disease a deficiency in dopamine is present in the striatum, secondary to degeneration of substantia nigra cells. In Huntington's disease due to loss of striatal interneurons, gamma-aminobutyric acid is reduced in the striatum. In tardive dyskinesia a state of striatal dopaminergic preponderance exists, perhaps related to an increase in the number of striatal dopamine receptors.

Treatment of Parkinson's disease is primarily directed towards enhancing dopaminergic transmission with levodopa and with dopamine agonists. The chorea of Huntington's disease and tardive dyskinesia improve with drugs which reduce brain dopamine transmission. In these disorders it is hoped that gabamimetic and cholinomimetic agents, and paradoxically also dopamine agonists, will result in useful symptomatic treatment.

SINCE THE INTRODUCTION in 1952 of chlorpromazine as an effective treatment of psychosis, several new effective antipsychotic agents have been developed. These drugs, like many other psychotropic drugs, can exert striking modifications on motor function in man through their effects on the extrapyramidal system. Also, psychotropic drugs are remarkably beneficial in the treatment of several neurological diseases characterized primarily by disordered motor function. To expose this influence of psychotropic drugs on motor function in man, this paper will review some aspects of the neurochemical pathology and treatment with psychotropic agents of two naturally occurring disorders of the basal ganglia — Parkinson's disease and Huntington's disease — and of the neuroleptic induced extrapyramidal syndrome, tardive dyskinesia.

Neurochemistry and Pharmacology of the Basal Ganglia

In the brain, the large subcortical nuclear masses known as the basal ganglia — caudate and putamen (striatum) and the globus pallidus — and the intimately related substantia nigra and subthalamic nucleus located in the upper brainstem, constitute the so-called extrapyramidal system. The physiology of this system is obscure but these nuclei appeared to be concerned with the modulation of somatic motor function.[1] The

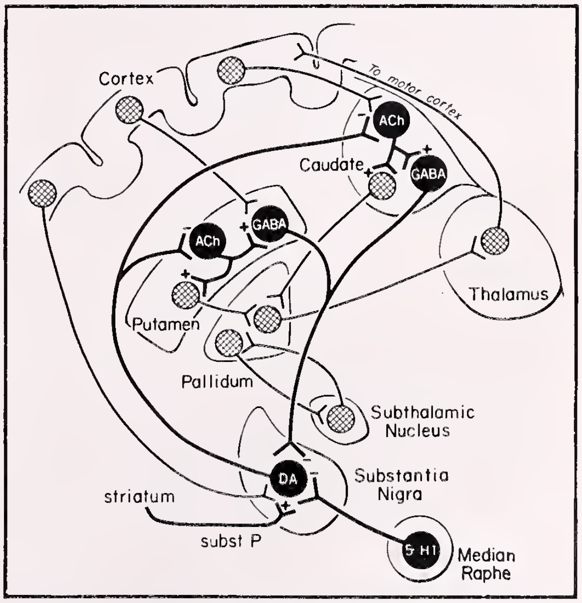

Figure — Schematic diagram of some postulated neuronal pathways in the basal ganglia.

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basal ganglia influence the motor cortex through a striatal-pallidal-thalamic circuit. The striatum in turn receives an important input from the substantia nigra and the cortex and the flow of information through the pallidum to the thalamus is modulated by the subthalamic nucleus.[2] In these nuclei several biologically active substances are present in relatively high concentrations. These include acetylcholine (ACh), the biogenic amines dopamine (DA), norepinepherine (NE), and serotonin (5-HT), and the amino acid gamma-aminobutyric acid (GABA). Also present, in these brain regions, in a parallel regional distribution are the enzymes which control the synthesis and degradation of these compounds.[3]

With the use of fluorescence and immunohistochemical techniques, a number of neuronal pathways have been delineated in the basal ganglia in terms of their neurotransmitter content (Figure). Best studied is the nigrostriatal pathway. Its DA-containing cells arise from the zona compacta in the substantia nigra and project to the striatum where they synapse with striatal interneurons which are cholinergic in nature. A pathway from the striatum back to the dopaminergic cells in the substantia nigra consists of the gabaminergic striatonigral pathway. McGeer[4] has also showed evidence for a pallidonigral gabaminergic system and the nigral cells further appear to receive input from cholinergic[5] and substance P containing cells[6] originating in the striatum as well as from serotoninergic ones from the median raphe nucleus.[7] Pharmacological and biochemical studies in experimental animals and in man have also shown that links exist between several of the neurotransmitter systems in the basal ganglia. For example, DA has mainly an inhibitory effect upon striatal cholinergic interneurons and ACh exerts mainly an excitatory effect on striatal dopaminergic mechanisms. Disturbance of the DA-ACh balance results in disorders of voluntary movement. Evidence for an interaction between other neurohumors in the basal ganglia such as the GABA-DA link, which are relevant to known disorders of the basal ganglia has been recently reviewed by Hornykiewicz.[8]

The activity of a given neuronal system in the basal ganglia can be modified under normal circumstances by a number of factors. Obviously it will be influenced by the input that it receives from other neuronal systems. For example, the gabaminergic striatonigral cells, as part of a neuronal feedback pathway, influence and modify through its inhibitory effect the degree of nigral DA cell activity (see diagram Figure). Another mechanism thought to be important in controlling the degree of activity of a given system is the feedback control mechanism mediated by presynaptic receptors. These receptors, also called autoreceptors,[42] are located in the presynaptic part of the neuron. For example, DA sensitive receptors exist in the dendrites, soma and probably presynaptic nerve endings of the DA nigrostriatal cells. Their stimulation by DA markedly reduces the firing rate of the DA cell and the subsequent release of DA at the nerve terminals in the striatum.[9] Through the stimulation of autoreceptors by its own neurotransmitters then, a neuron may regulate its degree of cellular activity.

The regulatory mechanisms, just described, are pharmacologically important. For example, it is well known that DA transmission can be attenuated by giving a DA receptor blocker, such as haloperidol. But a similar effect is also obtained by the administration of a gabaminergic agent which will inhibit dopaminergic cells or of a DA agonist such as apomorphine which suppresses the firing of nigral DA cells by stimulation of autoreceptors.[10] Conversely, enhancement of dopaminergic transmission in the striatum is produced by giving levodopa, a DA precursor, but could also be achieved by giving an antigabaminergic agent or possibly by blocking DA autoreceptors (with drugs such as chlorpromazine) which would stimulate the release of DA at the striatum.

Parkinson's Disease

Parkinson's disease is a disorder characterized clinically chiefly by hypokinesia, rigidity and tremor and impairment of righting responses. Dementia is also frequently present. The disease is progressive and the mortality of patients suffering from parkinsonism is three times that of the general population of similar age. In most instances the cause of the disorder is not known but recent evidence supports a genetic basis for Parkinson's disease with the pattern of inheritance following a polygenic model.[11] In a small group of patients parkinsonism appeared as a sequelae of encephalitis lethargia. In these patients the disorder tends to progress slowly and is frequently associated with oculogyric crisis as well as other abnormal physical findings on neurological examination. Signs of parkinsonism are also frequently encountered in patients receiving drugs such as phenothiazines and haloperidol and can be encountered, although rarely, with cerebrovascular lesions, head trauma, cerebral tumors, syphilis, carbon monoxide or manganese intoxication, in Wilson's disease and in Huntington's disease. Usually these forms of parkinsonism can be readily differentiated clinically from the so-called idiopathic variety.

In Parkinson's disease there is a degeneration of the nigral DA containing cells.[12] The major neurochemical consequence of this cell degeneration is a decrease in the concentration of striatal DA. Similarily the enzymes involved in the synthesis of DA, tyrosine hydroxylase and dopa decarboxylase, and the major DA metabolite homovanilic acid (HVA), are reduced in the striatum in Parkinson's disease. Also, GABA receptors which are thought to be located in the DA nigral cells, are reduced in the substantia nigra. These neurochemical abnormalities are accompanied by abnormally low concentrations of NE, 5HT and of the GABA synthesizing enzyme glutamic acid decarboxylase (GAD) in the basal ganglia.[3] Pharmacologically, also, a cholinergic preponderance seems to be present in Parkinson's disease.[13] This is thought to be secondary to decrease DA input on cholinergic cells, since it can be corrected, at least partially, by administration of levodopa.

The striatal "DA deficiency state" is thought to be the primary abnormality responsible for the patients major symptoms of rigidity and akinesia and the secondary cholinergic preponderance and the NE deficiency also probably contribute to the patients symptomatology. On the other hand, since a normal inhibitory effect of GABA and 5HT on DA nigral cells could aggravate Parkinson's disease it has been postulated that a functional deactivation of these chemical pathways exerts a beneficial compensatory effect in Parkinson's disease.[8]

Treatment

Even though anticholinergic drugs have been used in the treatment of Parkinson's disease since the beginning of the 19th century and are still widely used, the symptomatic treatment of this disorder is primarily directed towards enhancing striatal dopaminergic transmission. In 1961 Birkmayer and Hornykiewicz[14] administered the immediate precursor of DA, levodopa, I.V. to patients with Parkinson's disease and noted a transient but significant improvement in akinesia. In 1967 Cotzias[15] successfully introduced oral levodopa for the treatment of this disorder. Levodopa, while it does not alter the progression of the disease, has changed the outlook of the Parkinson's disease patient. It improves all symptoms of Parkinson's disease and is the most effective treatment that has ever been available for the disease. Currently it is administered in conjunction with a dopa decarboxylase inhibitor, carbidopa (in the U.S.). This enzyme inhibitor blocks the peripheral breakdown of levodopa to DA and successfully abolishes levodopa-induced nausea and vomiting in most cases.[16,17]

The use of levodopa in Parkinson's disease is frequently met with the appearance of some limiting side effects, mostly choreathetotic movements and mental disturbances.[15-19] Also, with the passage of time, usually after six to 12 months of treatment most patients on levodopa will show episodic reemergence of Parkinson's disease symptoms intermittently during the day ("on-off" effect), generally at the time when plasma dopa concentrations are low.[20]

In an attempt to circumvent some of these limitations drugs have been developed which act directly on DA receptors (dopamine agonists). Theoretically these DA agonists could offer several advantages over levodopa treatment. These agents: (1) are not dependent on dopa decarboxylase the enzyme which converts levodopa to DA and which is markedly reduced in advanced Parkinson's disease; (2) may be specific for different types of DA receptors; (3) may not form neurotoxic metabolites; (4) may not show an "on-off" effect if they have a long half-life.

Currently two groups of DA agonists have been employed in treating Parkinson's disease patients, the aporphines and ergolines. Both, the aporphine N-n-propylnoraporphine (NPA) and the ergot derivative bromocriptine, are the most promising antiparkinsonian dopamine agonists. Both exert, when given alone, potent anti-Parkinson's disease effects and can be beneficial in patients who fail to respond to levodopa. When combined with levodopa, the total daily dose of levodopa can be markedly reduced and the "on-off" effect is improved.[21,22] Unfortunately the dopamine agonists are not free of clinical side effects — they can also induce choreoathetotic movements and mental disturbances — and the consequences of their long-term administration to Parkinson's disease patients is not yet known, but the search for new specific DA agonists seems a most promising therapeutic field.

Huntington's Disease

Huntington's disease is an autosomal dominant neurological disorder characterized also by cellular degeneration in the basal ganglia and the cortex but with symptoms quite different from Parkinson's disease. It generally starts in the 4th or 5th decade of life and is characterized clinically by dementia, emotional disturbances and choreiform movements. Both males and females are equally affected. Although there is considerable variation, on examination Huntington's disease patients frequently show impairment of judgement, recent memory and calculations and later in comprehension, remote memory and vocabulary. Abrupt, purposeless, jerky and irregular movements are noticed. Sustained muscle activity is difficult and choreic movements may interfere with speech, swallowing, and breathing. Strength is normal. Muscle tone may be decreased but occasionally rigidity is striking. When Huntington's disease manifests itself in the 1st or 2nd decade of life (so-called juvenile or rigid variant of Huntington's disease) it may differ from the adult form considerably. There is an arrest in normal motor and mental development and then gradual deterioration with the development of spasticity, rigidity, dysarthria and dyspagia and severe dementia. Also rigidity and other Parkinson's disease-like features such as bradykinesia and propulsive gait can occur. Choreoathetotic movements may be absent. Cerebellar ataxia can be found and about 50% of the patients suffer from convulsions.[23]

Pathologically an extensive degeneration of the brain is present with decrease in brain weight and striking atrophy of the caudate nucleus and the cortex. Microscopically there is widespread cell loss in the striatum and deep layers of the cortex with reactive astrocytosis. Mild neuronal degeneration also occurs in the thalamus, subthalamic nucleus and hypothalamus, brainstem and cerebellum.[24]

The major neurochemical abnormality in Huntington's disease consists of a reduction in GABA and its synthesizing enzyme GAD in the basal ganglia.[25] This abnormality is thought to be secondary to degeneration of striatal interneurons. Although less consistently a decrease in choline acetyl-transferase is also frequently found in the basal ganglia.[26] Perhaps unexpectedly the concentrations of DA and HVA are normal in most cases of Huntington's disease except for a small reduction in the caudate nucleus. Recent studies have shown that gabaminergic receptors are normal or perhaps increased while cholinergic muscarinic receptors as well as dopaminergic receptors* are reduced in the striatum of Huntington's disease patients.[27]

Clinically the choreiform movements of Huntington's disease resemble the involuntary movements induced by levodopa in Parkinson's disease patients. Pharmacological evidence also suggests that striatal DA is important in mediating the chorea of Huntington's disease since drugs which enhance dopaminergic transmission generally aggravate chorea and conversely drugs which decrease DA availability of DA receptors consistently lessen choreiform movements. Consequently, it is currently postulated that a state of striatal dopaminergic preponderance underlies the chorea of Huntington's disease.[28] This may be a consequence of the reduced inhibitory gabaminergic input in the substantia nigra with subsequent enhanced striatal DA activity which further reduces acetylcholine release from cholinergic interneurons.

Treatment

Until recently the treatment of Huntington's disease has been mostly directed towards reducing striatal DA transmission either by depleting brain DA stored with reserpine or tetrabenazine, blocking DA receptors with phenothiazines and butyrophenones or preventing the synthesis of dopamine. Based on the recent neurochemical findings described above, efforts are now directed towards enhancing gabaminergic transmission. Since synaptic receptors for GABA are unchanged or perhaps increased in Huntington's disease, drugs which increase the concentration of GABA in brain or administration of GABA agonists are likely to result in improvement of chorea in Huntington's disease. While administration to Huntington's disease patients of the gabamimetic compound imidazole-4-acetic acid[29] and GABA itself plus diropylacetic acid (a compound thought to inhibit GABA transaminase) have not proven to be useful,[30] possibly these agents did not have an effect since neither GABA nor imidazole-4-acetic acid cross the blood brain barrier. Based on the reduction of cholineacetyltransferase in the basal ganglia, cholinergic agents have also been tried in Huntington's disease. The cholinesterase inhibitor physostigmine[31] has shown variable results, perhaps reflecting the decline in striatal muscarinic cholinergic receptors. Other cholinomimetic drugs though such as the acetylcholine precursor deanol have been reported useful[32] and choline salts may also reduce the abnormal movements of Huntington's disease.

It is hoped that the development of drugs capable of specifically activating acetylcholine and GABA receptors will provide a useful symptomatic treatment for Huntington's disease.

Tardive Dyskinesia

Tardive dyskinesia refers to a hyperkinetic syndrome related to neuroleptic therapy which, unlike other extrapyramidal side effects induced by these agents e.g. parkinsonism, akathisia and acute dystonia, may become permanent. Tardive dyskinesia consists of involuntary movements which are usually choreic or choreoathetotic in nature but the term also includes ballismus, dystonia and tics. Most commonly the involuntary movements involve the lips, tongue and jaw, constituting the so-called buccolinguomasticatory syndrome. Frequently choreic movements of the extremities are also present and at times, mostly in young patients, the dyskinesia are predominately axial. Signs of parkinsonism such as tremor and rigidity can coexist. The dyskinesias are aggravated by stress and reduced by sedation. Significant disability from them is rare[33].

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*Life Sci 21:1123, 1977.

Tardive dyskinesia occurs late in the course of treatment with antipsychotics, usually after two years of therapy, but can begin within three to six months of treatment. Strikingly they may start after a reduction or withdrawal of neuroleptics. Also characteristically they improve temporarily if the dosage of the antipsychotic agent is increased.[34]

Several risk factors have been mentioned but not confirmed for the development of tardive dyskinesia: old age, female sex, and previous organic brain damage such as frontal leukotomy or electroschock therapy. The presence of neuroleptic induced parkinsonism appears a well-established predisposing factor.[35]

The prevalence of tardive dyskinesia is not known. It is estimated that they are present in about 5 percent of a mixed psychiatric population on antipsychotic drugs. The natural course of this disorder is also unclear but it is now certain that tardive dyskinesia can persist indefinitely. Degkwitz[36] followed 273 patients with tardive dyskinesia for seven to 10 months after the discontinuation of antipsychotic agents and noticed that dyskinesia disappeared in 19 percent, was reduced in 19 percent, but did not improve in 62 percent. Crane[37] followed 37 patients for six to 26 months and observed a reduction in tardive dyskinesia in 10 percent and no improvement in 90 percent of the patients, after discontinuation of the neuroleptics.

Clinically tardive dyskinesia resemble levodopa-induced dyskinesia and the chorea of Huntington's disease. As discussed above, striatal DA overactivity is important in the mediation of these two conditions. This appears to be the case also in tardive dyskinesia since drugs which decrease DA transmission improve tardive dyskinesia while drugs which increase DA availability at DA receptor sites generally aggravate tardive dyskinesia.[38] The dysfunction of the nigrostriatal DA pathway by neuroleptics in tardive dyskinesia patients has been attributed to structural damage to the DA nigral cells,[39] although this has not been confirmed. Currently, since neuroleptics block DA receptors in the brain, it has been speculated that tardive dyskinesia results from a supersensitivity of postsynaptic DA receptors in the brain. This would explain why a reduction or discontinuation of neuroleptics aggravate the dyskinesia while a dose increase temporarily reverses it. Indeed in animal studies, chronic neuroleptic therapy can induce an enhanced behavioral response to dopaminergic agents. Such animals have been recently found to have increased numbers of striatal DA receptors which may account for the behavioral supersensitivity to DA receptor stimulants.[40] It is also possible that a blocking effect of the antipsychotics on the DA autoreceptors, which may increase the release of DA in the striatum, contributes to the production of tardive dyskinesia. An important role for the DA autoreceptors in mediating tardive dyskinesia is suggested by the suppression of tardive dyskinesia by the dopamine receptors stimulant apomorphine,[41] a drug which, at low doses, has been showed to act preferentially on presynaptic DA receptors.[42]

Of therapeutic significance is the observation that pharmacologically a state of cholinergic hypofunction is present in some cases of tardive dyskinesia,[43] as is also the case in the clinically similar hyperkinetic states of levodopa-induced dyskinesia and in Huntington's chorea. However, we have observed that intravenous injections of the cholinomimetic agent physostigmine can markedly accentuate the involuntary movements in some tardive dyskinesia patients. A state of "cholinergic hypersensitivity" may underlie the response of this subgroup of patients to physostigmine perhaps related to the potent anticholinergic effect of some antipsychotic drugs.[44] The possible role of other CNS neurotransmitters or neuromodulators in the production or mediation of tardive dyskinesia has not been adequately studied.

Prevention and Treatment — Once tardive dyskinesia is diagnosed an effort should be made if possible to discontinue the antipsychotic medications or to reduce it to its lowest antipsychotic dose. If the movements persist and are disabling, an attempt should be made to administer DA depleting agents such as reserpine or tetrabenazine (not available in U.S.).

In severe cases it might be necessary to use a neuroleptic agent such as haloperidol, but this will tend to perpetuate the abnormal hyperkinetic state. The anticholinergic antiparkinsonian drugs do not improve tardive dyskinesia and should be avoided in these patients.[34]

Current experimental approaches are directed towards: (1) enhancing striatal cholinergic activity, e.g. administration of deanol or choline salts;[46] (2) increasing central gabaminergic transmission, e.g. administration of the GABA transaminase inhibitor gama acetylinic-GABA or the GABA agonist muscimol; (3) decreasing dopaminergic activity through stimulation of DA autoreceptors[47] — both apomorphine and piribedil have been found to alleviate tardive dyskinesia. Recently we have observed improvement in three patients with tardive dyskinesia while receiving levodopa therapy. This paradoxical result, with potentially important therapeutic implications, might be explained by postulating that levodopa reduces striatal receptor sensitivity through excessive agonist supply with consequent normalization of striatal DA transmission. This is supported by experimental studies which show that levodopa reverses certain manifestations of DA supersensitivity induced by neuroleptics in animals.[48]

Every possible effort should be made to reduce the incidence of this syndrome. Antipsychotic agents should be given only when absolutely necessary and their use in the treatment of conditions such as psychoneurosis, depression and mania, and chronic pain syndromes should be discouraged. The smallest effective dose should be given for the shortest period of time possible. Drug "holidays" has been advocated to avoid continuous exposure to a potential toxin and to assess the effects of therapy. If during the treatment with antipsychotics parkinsonism occurs, it is desirable to avoid anticholinergic agents if possible since they may predispose to the development of tardive dyskinesia. Also, early recognition of the syndrome appears important since Crane[45] has suggested that discontinuation of antipsychotic drugs at the first sign of abnormal involuntary movements improves the prognosis for recovery.

Hopefully drugs will be developed with potent antipsychotic properties but no extrapyramidal side effects. Drugs acting mainly in mesolimbic and not striatal DA systems and drugs with significant antimuscarinic properties,[44] such as the newly developed diabenzodiazepine derivative clozapine,[46] might fulfill these expectations.

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"Minneapolis Skyline"

Dr. E. Theodore Palm, Minneapolis surgeon, is the artist of the beautiful watercolor on this month's cover. A previous watercolor "Minnehaha Creek" of Dr. Palm appeared on the August 1978 cover of MINNESOTA MEDICINE.

Doctor Palm is on the staffs of Fairview Southdale, Metropolitan Medical Center, and Methodist Hospital. He is a graduate of Gustavus Adolphus College and the University of Minnesota Medical School. He studied art at the Minneapolis School of Art.

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Impact of Psychotropic Drugs on Research in Psychiatry

JOHN M. DAVIS, M.D.* and MAURICE W. DYSKEN, M.D.*

Psychotropic drugs have had a pronounced effect on research in psychiatry. The impact of these drugs and the five major consequences are discussed: (1) the establishment of a new methodology, (2) the dopamine hypothesis of schizophrenia, (3) the norepinephrine, (4) serotonin theories of depression and (5) the research on blood levels of psychotropic drugs in psychiatric patients.

THE DISCOVERY OF PSYCHOTROPIC drugs has had a pronounced effect on research in psychiatry. First and foremost, it has lead to the formulation and adoption of a paradigm for psychiatric research which couples the principles of randomization and double-blind control procedures. Applications of this powerful paradigm have produced substantial empirical data that is of central importance to psychopharmacological theorizing. The discovery that particular diagnostic categories are benefited by certain classes of drugs has led to the formulation of the dopamine hypothesis in schizophrenia, and the norepinephrine and serotonin theories of depression. The clinical efficacy of these agents has served as a stimulus for research on blood levels to account for the divergent responses to psychotropic drugs. In this paper, five major consequences of the discovery of psychotropic drugs and their impact on research in psychiatry will be discussed and explored: (1) the establishment of a new methodology, (2) the dopamine hypothesis of schizophrenia, (3) the norepinephrine and (4) serotonin theories of depression and (5) the research on blood levels of psychotropic drugs in psychiatric patients.

In the early 1900s there was no effective treatment for schizophrenia, depression, mania and related mental disorders. In fact, 50 years later the only effective treatment for these conditions was electroshock therapy. Many patients who developed schizophrenia during adolescence or early adulthood spent the rest of their lives in mental institutions. The discovery of chlorpromazine in 1952 greatly altered the treatment of schizophrenia. As a consequence of this and other discoveries, psychiatric treatment is radically altered from what it was 25 years ago. Indeed, even the conceptual framework for psychiatric illness has undergone substantial change. These differences apply not only to biological aspects of the treatment of mental disorders, but also include such consequences as changes in their social and psychological treatments.

Chlorpromazine, synthesized as a member of the class of antihistamines, was first investigated by the French anthesiologist, Laborit, as a potential anesthetic agent. Laborit was primarily interested in the clinical properties of chlorpromazine, and encouraged his co-workers to experiment with this drug in a variety of situations. The French psychiatrists Delay and Deniker administered chlorpromazine to schizophrenic patients and observed highly beneficial effects. The drug appeared to be so effective that its use soon spread rapidly throughout the world. This drug and others like it have clearly altered the outcome of schizophrenia. Many patients who might have been hospitalized indefinitely have recovered, sometimes completely and within only a few weeks. Unfortunately, the results were not as favorable for all patients. Many showed significant improvement, but relapsed within a few years time, requiring additional treatment. Some would show a modest degree of recovery, yet on discharge showed some residual impairment; others continued to live their lives as chronic, long-term mental patients, but without further deterioration.

These results were clinically impressive, but advances in the field of psychopharmacology and new drug assessment demonstrated that in order for a drug to be proven effective, this must be established by a controlled trial. Several years after chlorpromazine was discovered, investigators performed carefully executed double blind studies to further verify the effectiveness of chlorpromazine. These early studies

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were important, not only for providing insight into the clinical effects of chlorpromazine, but also for providing evidence of significant therapeutic progress.

The principles of the controlled clinical trial were first applied in 1747 by Lind in an attempt to arrive at a suitable treatment for scurvy. While at sea, Lind isolated 12 patients with scurvy and prescribed a similar diet for each. In addition, six different treatments were tried using two patients for each treatment. Only those two patients who received lemons and limes recovered. Clearly, Lind had hit upon the principles of the controlled clinical trial. In brief, they may be described as the administration of different treatments to comparable patients who are studied simultaneously under controlled conditions, so that therapeutic results may be evaluated and compared.

The most important of the controlled clinical studies appears to be the extensive series of double blind trials conducted by the National Institute for Mental Health and the Veterans Administation. Of particular importance was the study by Cole, Klerman, and Goldberg[1] on the effectiveness of three antipsychotic drugs and a placebo for acute schizophrenic patients. Approximately 70% of the patients were helped substantially by antipsychotic drugs over a period of six weeks. For purposes of contrast, these findings may be considered within the historical context of studies on schizophrenia conducted prior to the discovery of psychotropic drugs. These studies show that a sizable proportion of schizophrenic patients became worse after entering the hospital; consequently, the major figures of psychiatry during this period characterized the course of schizophrenia as one of deterioration. In other words, many schizophrenics became symptomatically more severe after entering the hospital, and continued to run a down-hill course until they eventually stabilized with a severe illness. In the Cole, Klerman and Goldberg study about 45% of the schizophrenics treated with placebo continued to get worse. Deterioration of this sort had been common in schizophrenia, but was heretofore left untreated. It is of note that only a few patients who received a drug deteriorated. The highlights of these early studies were that: (1) antipsychotic medication seemed to check deterioration despite a poor prognosis, and (2) drugs produced a marked improvement in 70% of the schizophrenics treated.

Like schizophrenia, the latter is a chronic disease. The British Medical Research Council conducted a controlled study comparing streptomycin plus bed rest with best rest alone, and reported clinical improvement for each patient after the trial. Figure 1 shows the number of patients who fell into each category of improvement for the two drugs.

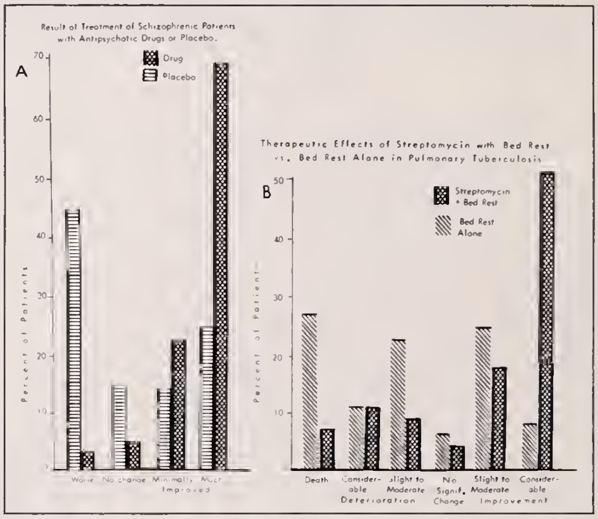

Fig. 1 — Results of treatment of schizophrenic patients with antipsychotic drugs or placebo.

The empirical data which has accumulated from the application of this paradigm in studies of pharmacological treatment for schizophrenia was the impetus for subsequent studies of the neurochemical basis of the effect. This research has implicated dopamine (DA), one of several neurotransmitters in the brain, as the neurotransmitter of most direct relevance to schizophrenia (Table 1). It is generally acknowledged that the neuroleptics which have been found to be effective in the amelioration of schizophrenic symptoms all exert their effect by blocking dopaminergic receptors.[3] Support for the DA hypothesis is, therefore, indirect evidence derived from the effectiveness of antipsychotic medications. One of the first antipsychotics, reserpine, is able to exert an influence on dopaminergic activity by blocking the storage of DA. As a consequence, the brain store of DA becomes depleted. However, reserpine has limited utility as an antipsychotic since depressive symptoms are a frequent side effect of the drug when administered in therapeutically effective doses.

Phenothiazines, butyrophenones, thiothixenes, indoles, and dibenzoxazepines are classes of antipsychotic drugs of proven efficacy which exert their beneficial effect on schizophrenic symptoms by blocking dopamine receptors. This blockade is established by the competitive advantage of these molecules in occupying receptor sites normally occupied by DA. As the clinical potencies of these agents are highly related to the ability of the agent to be bound to a DA receptor

TABLE 1

Dopamine Hypothesis in Schizophrenia

Pharmacologic Attention	Clinical Correlate	Functional Effect on Dopamine
1. Antipsychotic medication	Clinical improvement by dopamine receptor blockade	↓
2. Reserpine adminIstration	Clinical improvement by dopamine depletion	↓
3. L-Dopa administration	Clinical worsening by increased functional dopamine	↑
4. Dopamine agonists given to schizophrenic e.g. amphetamines, methylphenidate	Clinical worsening by increased functional dopamine	↑
5. Dopamine agonists abused by non-schizophrenic	Paranoid psychosis	↑

in vitro, there is a good deal of indirect, pharmacological evidence to support DA as the major neurotransmitter involved in the mechanism by which antipsychotics benefit schizophrenics.

There is additional indirect evidence available that Parkinson's disease, the etiology of which is known to involve decreased levels of DA, is mimicked by certain extrapyramidal side effects of the neuroleptic drugs. Galactorrhea, another side effect, results from increased prolactin secretion which is under dopaminergic control. There is some evidence (Figure 2) that a mininal antipsychotic dose to induce serum prolactin elevations may correlate with the does required for effective treatment.

Collateral evidence for the role of DA in schizophrenia may also be derived from studies concerning the effects of dopamine agonists. Cocaine, amphetamine, methylphenidate and other psychomotor stimulants produce a psychotic syndrome which is indistinguishable from paranoid schizophrenia in some subjects who lack a prior history of this disorder. The development of the syndrome depends upon the chronic administration of large doses of these stimulants which all act directly on dopaminergic systems by stimulating the release of DA and/or block reuptake of DA. The phenothiazines and the butyrophenones, as well as other DA receptor blocking agents, prevent amphetamine euphoria in human subjects, as well as the development of DA mediated stereotypic behavior in animals. Stereotypy, a syndrome involving the constant repetition of stylized motor activity, is usually considered as an animal model for schizophrenia. The antagonism of stereotypy is an important quality of new drugs which are screened for neuroleptic activity. This antagonism occurs at doses which are therapeutically effective in human subjects.

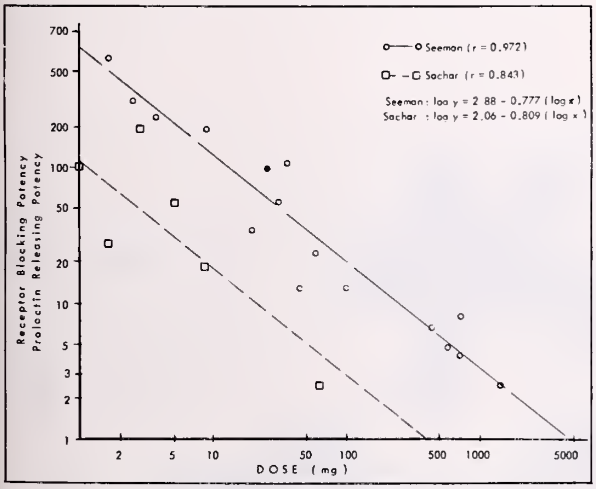

Fig. 2 — Clinical potency of these drugs is represented on the abscissa, while their dopamine blockade and prolactin increasing potencies are represented on the ordinate.

The acute administration of small doses of these stimulants does not produce a psychosis but is capable of producing a temporary exacerbation of schizophrenic symptoms in psychotic subjects. Clinical deterioration may also be produced by augmenting the functional dopamine reservoir in other ways. L-DOPA, a precursor of DA, can produce such deterioration when given in sufficient doses. MAO, an enzyme which inactivates DA, could effect the dopamine reservoir by altering the rate at which DA is metabolized. Several laboratories have shown that the levels of platelet MAO in chronic schizophrenic populations are depressed. Lower levels of MAO would help increase brain levels of dopamine by slowing the rate at which it is metabolized.

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Taken together, the studies on the effects of neuroleptic drugs and those on psychomotor stimulants provide indirect, but persuasive evidence for a major role played by the dopaminergic systems in the onset and maintenance of schizophrenia. This work is a direct result of the application of modern research paradigms to the study of pharmacological interventions in schizophrenia. The demonstrated utility of certain classes of pharmacological agents in the treatment of schizophrenic disorders has opened the way for the fruitful investigation of the pharmacologic activity of these agents. Such research continues to provide critical evidence for the elucidation of the biochemical alterations which accompany schizophrenia.

Just as the demonstration of the effectiveness of neuroleptic pharmaco-therapy in schizophrenia has lead to research on the mechanism of these drugs, so too, has research evidence on the efficacy of various treatments for depression stimulated work on their relationship to various neurotransmitters (Table 2).

Recently there have been major advances in our understanding of the important neurochemical events in depression.[4,5] Drugs such as the tricyclics and the monoamine oxidase inhibitors, in addition to electroconvulsive therapy (ECT), are known to raise norepinephrine (NE) levels. Specifically, the tricyclic drugs block the reuptake of norepinephrine (NE) and serotonin, inactivating the mechanism by which these amines are metabolized. Consequently, more transmitter substances remain at the receptor site for a longer period of time, resulting in a potentiation of NE and serotonin. The MAO inhibitors block the enzymatic destruction of NE and serotonin which raises brain levels of these substances. There is excellent evidence that ECT (electroconvulsive treatment) benefits depression. The mechanism by which it does so is less clear than for the drugs mentioned above. There is evidence from animal studies that the rate of synthesis of NE, serotonin and dopamine is accelerated by electro-shock treatment. Interestingly enough, shock treatment of depressed patients also suffering from Parkinson's disease produces a marked improvement in the latter which parallels the time course of the improvement of the depression.[6] The synthetic pathway of DA and NE, the presumed transmitters involved in Parkinson's disease and depression, starts with tyrosine. The pathway is tyrosine-dopa-dopamine-norepinephrine. The rate-limiting factor for these steps is the tyrosine to dopa step. Hence, since Parkinson's disease improves, the presumption is that improvement is a consequence of increased DA synthesis. In those pathways where DA is converted to NE, NE levels would also increase. While this hypothesis of the therapeutic mechanism of ECT treatment is consistent with available evidence, including that from drug studies, there is as yet no definitive evidence for this hypothesis. Nevertheless, it seems likely that both NE and serotonin are implicated in depressive illness.

As with the effect of the neuroleptics on DA, the evidence for the effects of treatments for depression is derived from indirect methods. Brain norepinephrine is metabolized entirely to MHPG. Norepinephrine derived from the peripheral nervous system is metabolized to normetanephrine, VMA, and only partially to MHPG. Thus, urinary MHPG is thought to be a marker for brain MHPG. MHPG levels in depressed patients have been reported as reliably lower than levels in comparable control groups.[7,8]

A second strategy, that of administering drugs which lower NE in depressed patients and controls, also provides support for the relationship between NE and depression. Reserpine, a drug commonly used in the treatment of hypertension, has been reported to produce episodes of depressive symptomatology in

TABLE 2

Norepinephrine Hypothesis in Depression

Pharmacologic Attention	Clinical Correlate	Functional Effect on NE
1. Antidepressant medication	Clinical improvement by increasing functional norepinephrine	
a. Tricyclics	Inhibition of re-uptake	↑
b. MAO — I's	Inhibition of MAO metabolism	↑
2. ECT	Clinical improvement by enhancement of norepinephrine synthesis	↑
3. Reserpine	Clinical worsening by norepinephrine depletion	↓
4. Alpha methyl DOPA	Clinical worsening by norepinephrine depletion	↓

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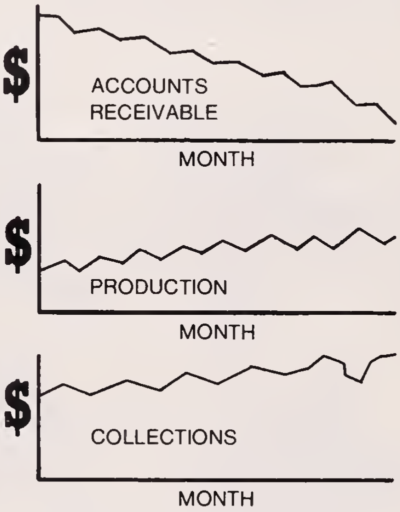

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persons who have known history of this disorder. Alpha-methyl-dopa, a drug which lowers NE levels in the brain by a different mechanism than reserpine, can also produce depressive symptoms. Much the same evidence can also be used to support the serotonin theory. The tricyclic antidepressants, in general, inhibit the reuptake of serotonin, MAO inhibitors block the metabolism of serotonin, reserpine lowers brain serotonin level, etc. Thus, we have a norepinephrine theory of depression which states that manic patients may have high levels of norepinephrine and that depressed patients may have low levels of norepinephrine. Similarly, the serotonin theory states that manic patients may have high levels of serotonin, and depressed patients may have low levels of serotonin.

NE may not, however, play a central role in all depressions. Studies have shown that some depressed patients excrete reduced levels of a CSF component known as 5-hydroxy-indolacetic acid, a metabolite of serotonin. These patients have been shown to improve with the administration of the serotonin precursors 5-hydroxy-tryptophan and tryptophan. There is also some evidence to suggest that serotonin and NE depressions show their greatest treatment response to different varieties of the tricyclic antidepressants. These varieties are relatively more specific in their effects on these two neurotransmitters. Further, although definitive evidence is lacking, it is hypothesized that amitriptyline is most effective for serotonin depressions, and that imipramine, desimipramine, protriptyline and nortriptyline are most effective for norepinephrine depression. It would follow that if a patient is not responsive to a given tricyclic and needs to be tried on a second tricyclic, a patient tried on the latter four should be switched to amitriptyline, and vice-versa.

In view of the above considerations, attention should be focused on subgroups of patients who have normal 5HIAA and low MHPGs and low 5HIAA, and normal MHPG. It has been suggested that there may be several different causes of depression. One cause may be low brain norepinephrine, while another cause may be low brain serotonin. Thus, depression may be a general category of disease, but which includes several different etiologies, such as low norepinephrine depressions, low serotonin depressions and possibly others. There is also evidence that depression may result from an imbalance in transmitters; it has been found that most physiological systems are controlled by a balance between transmitters. For example, autonomic functions of the peripheral nervous systems are controlled by a balance between acetylcholine and norepinephrine. If depression is a disease of the central autonomic system involving norepinephrine, it may be that on a central level, a balance between norepinephrine and acetylcholine caused depression. The balance hypothesis has been suggested by Janowsky and his coworkers[9,10] who state that depression may be a function of high acetylcholine, low norepinephrine, and mania a function of low acetylcholine, high norepinephrine. They support this theory with the observation that agents which raise brain acetylcholine have an antimanic effect and can also produce depression in some patients. Space does not allow a detailed consideration of the biochemical causes of mania and depression. The importance of the argument here is that the discovery that depression could be benefited by several different drugs, or caused by several different drugs, permits pharmacologists and biochemical psychiatrists to examine pharmacological mechanisms. This has resulted in the formulation of the catecholamine theory of depression, and provides tools for elaborating the etiology of these conditions. A consequence for psychiatric theory of the discovery of drugs which benefit these conditions are these theories as to what may be causing the disorders at the biochemical level. We have not as yet validated these hypotheses concerning causation. They remain at present supported by some, but not absolutely all, available evidence. One of the most important consequences of these psychotropic drugs is the description of their biochemical mechanisms of action, and the implications they have for the development of plausible causative theories of mental disease. The norepinephrine, serotonin, acetylcholine theories of depression and the dopamine theory of schizophrenia, in particular, provide focus and direction.

The final area in which psychotropic drugs have exerted an impact on research in psychiatry is the study of relationships between plasma levels and therapeutic response.[11] Initial studies in this area have exposed the wide range of individual differences in plasma levels observable with the same dose of the same drug. These differences may be investigated in their own right, and may have a substantial impact on the outcome of treatment with these agents. In view of such differences, it should be noted that plasma levels of psychotropics, psychotics, tricyclics, MAO inhibitors, and lithium show a decided relationship with therapeutic response and side effects. The importance of this relationship can be appreciated only if plasma levels help the physician to anticipate treatment consequences that are not foreshadowed clinically. Because most psychotropic drugs require a week or more in which to produce discernible effects, information as to the probable treatment consequences for early plasma levels has clinical applications of potential importance. If treatment response is correlated with plasma levels, the physician may move rapidly to achieve an effective plasma level. Judgments in regard to dosage adjustments need not be suspended until a clinical response, or its absence, becomes manifest.

In addition, monitoring plasma levels might be used to prevent toxicity. Workers in Scandinavia and in the United States have demonstrated wide variation in plasma levels for the tricyclic antidepressants. Studies of the degree of inhibition of platelet monoamine oxidase have demonstrated similar individual differences in how the body handles MAO inhibitors so that here again plasma levels vary substantially, requiring that the dose be adjusted clinically. There are also wide differences in lithium plasma levels of patients given identical doses. The bottom line for the clinician is that, since different patients metabolize drugs at different rates, different amounts of drugs reach the brain. As a consequence, the clinician must vary the dose in accordance with the clinical response to obtain the optimal results. Our growing knowledge of clinical pharmacology should furnish assistance in rendering such judgments.

Potentially, then, plasma levels may serve an important role in shortening acute treatment intervals. They may also help in identifying those who have failed to show adequate acute responses because of insufficient dosage. There are patients who have a history of nonresponse to psychotropic drugs and some of these patients may demonstrate an inability to achieve adequate plasma levels on standard therapeutic doses. These patients deserve a trial at higher doses.

Unfortunately, not all nonresponders will benefit from a more vigorous treatment strategy. Here, too, plasma levels may come to play an important role. Studies of butaperazine, a neuroleptic used in the treatment of schizophrenia, have shown that maximum clinical response is achieved at plasma levels that are neither too low nor too high.[12] Thus, increasing the dose is not an appropriate response to treatment failure in all cases. Some patients who show no response after an adequate trial of a given dose of a psychotropic drug may do so on a higher or a lower dose. It is not yet known whether other psychotropic drugs show this inverted-U relationship between plasma levels and clinical response as does butaperazine. It therefore remains an interesting topic for research to verify the presence of such relationships for other psychotropics, especially if the effective range of plasma levels, the ''therapeutic window'', is a small one.

Plasma levels, insofar as they are correlated with treatment response, are of potential use to the practitioner in adjusting initial drug dosages, particularly if the therapeutic window is small. Moreover, as the therapeutic window narrows, the role of individual differences in the metabolism and distribution of the drug en route to critical brain areas assumes increasing importance. Plasma level studies which have focused on inter-individual variation of this sort have recently begun to yield important information.

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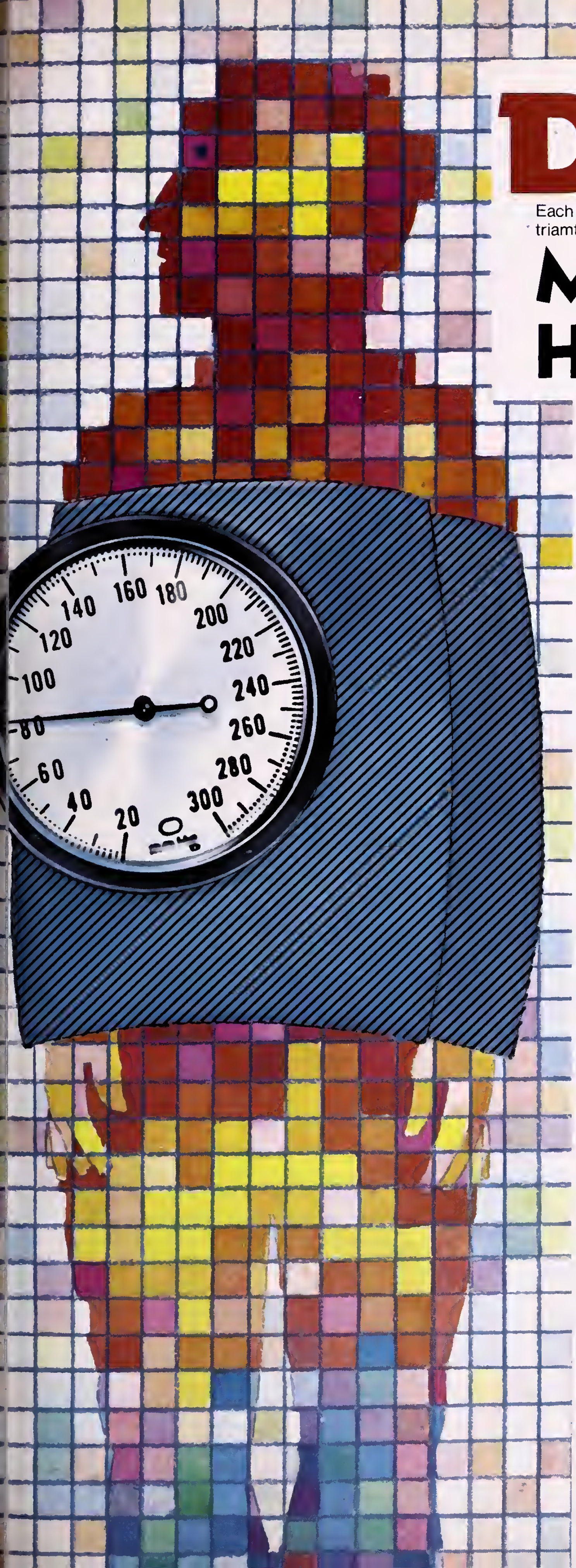

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Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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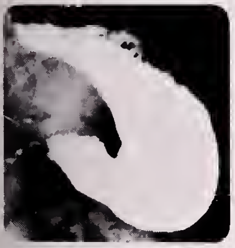
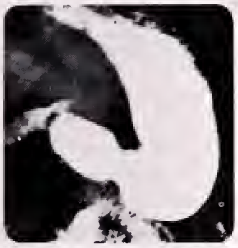


Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

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*This drug has been classified "probably" effective in treating certain functional G.I. disorders.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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> Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:
>
> May also be useful in the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis, acute enterocolitis, and functional gastrointestinal disorders); and in neurogenic bowel disturbances (including the splenic flexure syndrome and neurogenic colon).
>
> THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.
>
> For use in the treatment of infant colic (syrup).
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> Final classification of the less-than-effective indications requires further investigation.

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Usual Dosage: Bentyl 10 mg. capsule and syrup: *Adults:* 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children:* 1 capsule or teaspoonful syrup three or four times daily. *Infants:* ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg. *Adults:* 1 tablet three or four times daily. Bentyl Injection: *Adults:* 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

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Index to Advertisers

Anderson, C. F. Co. 86
Beltone Electronics Corporation 78
Burroughs-Wellcome Co. 132
Classified Advertising 128
Fidelity Professional Services 114
Finley & Friday, Inc. 112
Lilly, Eli & Co. 74
Mead Johnson Pharmaceutical Division 107, 108
Medcalf Orthopedic Appliances 140
Medical Protective Company 114
Merck Sharp & Dohme 90
Merrell-National, Inc. 86, 87, 118, 119, 120, 131
Minnesota Medical Association 76
Pfizer Pharmaceuticals 72
Purepac Pharmaceutical Co. 139
Roche Laboratories .... Cover 2, Covers 3, 4
Smith, Kline & French 117
Trautmans 120
Upjohn Company 88, 89, 90
Warner/Chilcott Labs 96

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Special Article

The Case for "Brain Death" Legislation
A Response To The Critics

WILLIAM H. MANNING, J.D.,* and HOWARD J. VOGEL, J.D.†

The 1979 Minnesota Legislature will again consider legislating the concept of "brain death." Controversy about this proposal is prompted by confusion of the issues involved. Arguments of the opponents of brain death are answered.

IN 1977, THE MINNESOTA Medical Association, following lengthy deliberation and a recommendation by its Ad Hoc Committee on Death, proposed to the Legislature of the State of Minnesota that legislation be considered to legalize the concept of "brain death."[1] At hearings before the Senate Judiciary Committee, strong opposition to the proposal was voiced by the Minnesota Catholic Conference and Minnesota Citizens Concerned for Life, with the result that the proposal was tabled for the 1977 legislative session.

The issue, however, did not die. Once again, the 1979 Legislature will take up the issue of "brain death," this time considering enactment of the Uniform Brain Death Act drafted by the National Conference of Commissioners on Uniform State Laws.[2] The proposed act states:

> For legal and medical purposes, an individual who has sustained irreversible cessation of all functioning of the brain, including the brain stem, is dead. A determination under this section must be made in accordance with reasonable medical standards.

As before, the Minnesota Medical Association supports enactment of this language.[3] Once again, as well, objection to this legislation is anticipated from those who opposed "brain death" legislation in 1977.

The conflict surrounding this legislation reflects a broader, continuing controversy in the larger society over issues related to death and its processes and to questions of care and treatment of the terminally ill. This controversy is evidenced by the many newspaper and magazine articles, symposia, conferences, books and speeches devoted to these subjects in recent years.

Much of the 1977 dispute over brain death legislation involved a mistaken understanding of the issues, leading to confusion about the intent of such legislation. This article will attempt to shed light on the subject of "brain death" by setting the legislative dispute in its proper context and, in that context, answering the most common arguments of those in Minnesota who oppose legislation espousing the concept of "brain death."

It should be understood that, in the opinion of the authors, important theological and philosophical questions about life, death, the quality of life, and the nature of human personality are raised by the brain death dispute.[4] We will not, however, deal with such questions. They have provided the substance of intellectual argument throughout the centuries. Our society has not yet found answers to these questions, and we seriously doubt whether ultimate answers to such questions can be perfectly discovered by human reason or intuition.

In the meantime, physicians, families, judges and other important actors in the human drama of health care are daily called upon to perform their roles under circumstances in which their specific responsibilities to a patient are defined by the answer to the question, "Is this person dead?" Dramatic advances in medical science, discussed more fully below, have led to a situation in which the traditional criteria for determining the occurrence of death — absence of pulse and respiration — are no longer, in all cases, reliable. To these traditional criteria, the concept of brain death adds an important, scientifically reliable criterion for determining when death has occurred. For that reason, we believe that society must come to grips with "brain death" through enacting that concept into legislation.

Medical Context

For many years, the problem of defining death involved a simple medical judgment, made by a physician at the deathbed. Medical criteria for determining when death occurred were easily applied by physicians and seldom, if ever, questioned. There was no statutory definition of death because there was general agreement on what it was. According to common law, developed by the English and American courts, death is a moment when life ceases,

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*Dorsey, Windhorst, Hannaford, Whitney and Halladay, Minneapolis

†Associate Professor of Law Hamline University School of Law, St. Paul, Minnesota.

> . . . defined by physicians as a total stoppage of the circulation of the blood and a cessation of the animal and vital functions consequent therein, such as respiration, pulsation, etc. . . .[5]

For many years, society as a whole accepted this definition of death.

Into this relatively simple scene, Twentieth Century technology thrust its way, and two advancing areas of medicine — resuscitation of dying patients and transplantation of organs — converged on the deathbed to create the current concern over legislating the concept of "brain death." Medical technology now permits the resuscitation of many dying patients and the maintenance of those patients on sophisticated machinery. For the first time, we are able to maintain discrete bodily functions such as respiration and cardiac activity — functions normally dependent upon the brain — separate from and in the absence of brain function. In other words, we can maintain a body in a state of functional decapitation.[6] Furthermore, physicians are now able to transplant organs from one person to another, saving many lives which might otherwise be lost to the ravages of organic disease.[7] The response to these advances in several states has been the passage of "brain death" legislation.[8] Minnesota is now being asked to follow suit by enacting the Uniform Brain Death Act.

Minnesota Legal Context

During the past year, three cases in Minnesota courts have provided our State with first hand experience in the problems associated with brain death. One of these cases, involving four year old Stacey Ellison, received prominent newspaper coverage.[9] Stacey Ellison sustained irreversible brain damage from severe head injuries inflicted by an assailant. She was placed on a respirator. Upon determining that Ellison was "brain dead" according to current standards, St. Paul Children's Hospital medical personnel signed a death certificate and requested an order from the Ramsey County District Court permitting them to remove the child from the respirator. In a two day hearing, the court received uncontroverted medical testimony that Stacey Ellison had suffered irrversible brain death; the court subsequently issued its order permitting removal of the respirator. An emergency appeal to the Supreme Court of Minnesota resulted in an order affirming the District Court. The child's heart stopped beating shortly after the respirator was turned off.

In a Minnesota criminal case, cited by the Ellison court, the concept of brain death was judicially recognized. The defendant in *State v. Gerszewski* was charged with murdering John Malchow by setting fire to his apartment. The victim was taken to Hennepin County Medical Center, placed on a respirator, and treated for burns. Medical examination subsequently showed that the victim had suffered irreversible brain death and the respirator was disconnected. Malchow's heart ceased functioning shortly thereafter. Following his indictment, the defendant filed a motion to dismiss the indictment on the grounds that Malchow's death was caused by disconnection of the respirator, not by the actions of the defendant. In denying the defendant's motion, the court adopted the concept of brain death.[10]

The third case involved a patient at Hennepin County Medical Center, Hazel Soderquist, who was placed on a respirator after suffering a heart attack. Subsequent medical examination revealed that she had not suffered irreversible brain death, but was, instead, in a deep coma. Soderquist had suffered irreversible damage to the higher centers of the brain, but her brain stem remained intact. Thus, her condition was similar to that of Karen Ann Quinlan, whose case has been nationally publicized. Medical personnel, unable to locate Soderquist's relatives, sought and received an order from the court permitting them to remove the respirator even though she was clearly not medically dead.[11]

Proper Scope of Brain Death Dispute

It must be kept in mind at the outset that the concept of brain death deals only with the question, "When is a person dead?" It emphatically does not address the question, "When should a person be allowed to die?" Much confusion has arisen between these two questions because of widespread publicity surrounding a few notorious cases, most notably *In re Quinlan*.[12]

The Hazel Soderquist situation is similar to that of Karen Ann Quinlan; neither of these persons was "brain dead" when their cases came before the court. The case of Stacey Ellison, on the other hand, is quite different from both of these because it did present a clear case of "brain death."

A comparison of Karen Ann Quinlan's situation with that of Stacey Ellison will illustrate the difference between the questions, "When is a person dead?" and "When should a person be allowed to die?"

Karen Ann Quinlan does not today and has never met the accepted medical criteria for being "brain dead."[13] Total brain function is *not absent* in her case. Rather, the brain stem, which was not totally destroyed by the cerebral accident Quinlan suffered, continues to function and to maintain respiration and cardiac activity without support from technological equipment. The legal question which arose in *In re Quinlan* was whether or not Quinlan, who was at that time sustained by life support equipment, should be removed from that equipment so that natural processes could take their course. It was not known whether Quinlan would live or die once support systems were removed. The case was brought to court by Quinlan's parents because Quinlan had no hope of recovery and the parents felt that the quality of her life was below the level of human dignity; consequently, it was argued, she should be removed from supporting equipment so that death could occur if it would. It was never contended that Quinlan was dead. Rather, her situation was characteristic of what is known as "a persistent vegetative state." As we all now know, death did not occur once the life support systems were removed; Karen Quinlan continues to live in a nursing home in a deep coma, showing signs of brain activity which negate the possibility of her being found dead under the Uniform Brain Death Act. Similarly, the Hazel Soderquist situation presented the court with the question of whether or not the medical personnel in attendance should be permitted to withdraw life support systems which maintained Soderquist in a persistent vegetative state.[14]

The case of Stacey Ellison, by contrast, presents strikingly different facts.[15] Stacey Ellison was the subject of a battering incident. Several hours after her admission to the hospital (once her condition had stabilized with assistance from circulatory and respiratory support systems), neurological examination reflected that she had suffered severe brain damage and that, in fact, there was no evidence of any functioning of the brain. Thus, Stacey Ellison had suffered an injury which caused the total destruction of the brain, which occurs when massive intracranial pressure, due to injury, exceeds the systolic blood pressure and causes blood flow to the entire brain to cease, both to the higher centers via the carotid circulation and to the lower centers via the vertebrobasilar circulation.[16] Once blood flow ceases, all brain functions cease shortly thereafter. Thus, in the Ellison case, the question presented to the court was whether or not the permanent loss of all brain function constitutes death; in other words, "Was Stacey Ellison dead?" The question was not, "Should Stacey Ellison be allowed to die?"

The distinction between these two situations is critical since it appears that some of the objections to enactment of the brain death concept are based upon misunderstanding of the questions raised by each situation.

Answers to Arguments Raised by Opponents of Brain Death Legislation

The opponents of brain death legislation do not challenge the validity of the concept of brain death. In fact, they agree that someone who meets the criteria for brain death is, in fact, dead.[17] But the opponents do contend that the concept should not be enacted into legislation. Some of their arguments are based upon timeliness, while others are based upon substantive objections. Keeping in mind the fact that brain death deals only with the question, "Is this person dead?", we will examine the opponents' arguments one by one.

The Proposal is Premature; Society and Physicians are Not Familiar with the Concept of Brain Death

Those opposed to brain death legislation argue that society does not understand and has not accepted this concept, and that legislation on this subject would go beyond the wishes of the general public. They assert that the definition of death should be allowed to evolve in the social process because the issue is highly complex and emotional. They argue that enactment of legislation to define death would be an overreaction to advancing medical technology; and they contend that the Minnesota Legislature should, instead, carefully observe the ramifications of brain death legislation in other states before legislating on this subject.

There is no question that further public discussion of this issue is desirable. But the critical questions are whether, and at what point, the legislative process should attempt to provide a clear and concise standard for determining that death has occurred. We have already pointed out that cases are currently being litigated to challenge current notions of death. There is no reason to assume that such litigation will cease in the near future.

Those who must act based upon whether or not a person is dead currently do so in a terrain with no legal maps. In the absence of clear guidelines, accepted under law, these persons needlessly face the possibilit
of lawsuits which can only deter them from accepti
their responsibility to declare "brain dead" pers
dead. Official action, not mere discussion of
issues, is required to eliminate the existing c
between current medical practice and present

The legislative process itself provides an e
arena for public discussion of and educatio
subject of brain death. That process provide
opportunity to separate and delineate the
single forum, so that the debate and event

are based on enlightened and informed viewpoints rather than upon quick emotional reactions.

Opponents of brain death legislation also contend that a statute defining when death occurs is unnecessary because society has not previously had one. But we see the absence of a statute defining death as nothing more than testimony to the relative simplicity of the past compared to the present. A statute was not necessary because we lacked the ability to resuscitate and keep alive parts of the body in the absence of a functioning brain. Thus, brain death is a modern phenomenon brought about by advances in medical technology. Our current ability to sustain, indefinitely, a person whose brain is dead raises issues which could not have arisen fifteen or twenty years ago.

The Proper Forum for Settling the Definition of Death is in Court, Not in the Legislature

Opponents of brain death legislation argue that questions about when death occurs should be settled through court decision, not through the legislative process. We disagree.

We have already observed that the legislature is a most fruitful arena for societal discussion and action on this issue. Asking the courts to define death constitutes an abdication by the people of their right to deal with questions of great public concern through their elected legislative representatives. Such abdication of citizen responsibility can only lead to government by the judiciary — a result neither countenanced by the founders of this republic nor sought by most of the judges who preside over its courts.

Resort to litigation to resolve an issue as pressing as when death has occurred is fraught with difficulty. The courts are not eager for this role, and have, in fact, requested the legislature to take action on this subject.[18] Courts seldom, if ever, have all facts and arguments before them in a specific case. Their access to facts and arguments hinges largely upon the skill of the lawyers involved, the lawyers' awareness of the issues, their thoroughness, intellectual capacities, and bility to communicate. Often, courts are asked to ake decisions about a patient without anyone present epresent the interests of the patient.[19] The litigation ess simply does not allow for the full and complete of all sides of an issue before a decision is ed. A court makes a decision based upon the one particular case, not upon wider theoretical, hical, or medical grounds. Rarely does a ase before the court present all the socially acts and arguments necessary to make s for society. In most cases the decisions of courts are limited to the facts of the specific case itself and are not easily capable of general application. And, finally, court decisions are based upon precedent, and there is no assurance that precedent will develop in an acceptable direction.

In light of these considerations, continued reliance upon the courts to define when death has occurred only forestalls the day when the Legislature will, almost inevitably, be required to take up the issue and devise a statute which reflects our best current understanding.

Physician Fear of Legal Liability for Declaring a Person "Brain Dead" is Unfounded; Therefore, a Definition is Unnecessary

Opponents of legislating the brain death concept argue that physician fear of legal liability (one of the major arguments used by the proponents) is totally unfounded, since no physician has ever been found liable for pronouncing a person "brain dead."

Whether or not a physician has ever been found liable does not diminish the fact that such fears are real and important. Many physicians are advised by the hospitals at which they work not to discuss the concept of brain death for fear of provoking lawsuits. The opponents overlook the substantial burden upon the physician's personal and family life, and upon the physician's ability to care for patients, created by involvement in a lawsuit, regardless of the outcome. Ultimate financial liability is much less destructive than the cost in psychic energy, time, effort and legal fees devoted to defending a lawsuit. Unfortunately, there is currently no way to prevent a disgruntled relative from filing a lawsuit against a physician, which the physician must then defend.

Tucker v. Lower[20] is one instance in which a physician was subjected to litigation which would have been precluded had there been a brain death statute in Virginia. In that case, physicians on a transplant team were sued for $100,000 by William Tucker, whose brother's heart was removed on May 25, 1968. The plaintiff claimed that the operation was commenced before his brother died. Though the injured brother had shown normal pulse and normal blood pressure while on a respirator, the neurologist's examination showed that the brother was neurologically dead, and support systems were terminated. The judge permitted the jury to consider all causes of death, including injury to the brain and cessation of breathing or heartbeat. A verdict was returned for the defendants, but *Tucker* demonstrates why physicians fear entanglement in the legal arena. Whether this fear is rightly or wrongly founded, physicians frequently resort to the courts to obtain legal authority to terminate support systems to a brain dead person, as they did in the Stacey Ellison case.

Physician fear has, in the past, led either to inaction when confronted with brain death, prolonging the anguish of uncertainty to the loved ones of the brain dead person, or to resort by the physician to the courts for permission to declare a person brain dead, thus wasting court time and client money. Brain death legislation will remove the possibility of litigation in these cases, providing a remedy for these two problems.

The Current Medical Standard of Brain Death Provides Sufficient Certainty in the Determination of Death

Opponents of brain death legislation argue that a statute is unnecessary because the community medical standard is sufficient to protect physicians and meet society's need for a definition.

Despite the fact that some courts and legislatures have adopted the concept of brain death, in Minnesota confusion remains because our law gives no certain answer to the question, "Is this person dead?" Issues involving planning for and actual disposition of property upon death require legal certainty about the cause and time of death. The same is true in assigning responsibility for death under the criminal law. Thus, the question of whether and when a person is dead plainly seems to be one which demands legal clarity. The law requires an answer to this question in a variety of contexts: in determining whether or when to bring a murder or manslaughter charge; in determining cause of death; in determining whether or not there are survivors of the possible decedent; in determining, for purposes of a will or insurance, which of two persons died first; and other, innumerable contexts. Reportedly, some murder prosecutions have been foregone due to prosecutorial reluctance to pursue the case in the absence of a more reliable definition of death.

Although the House of Delegates of the Minnesota Medical Association, consisting of 104 elected physician representatives from throughout the state, adopted the proposed brain death legislation unanimously, there is no doubt that some physicians could be found to testify that brain death is not the common standard. Such uncertainty in the law, in such a vital area, is intolerable.

Enactment of Brain Death Legislation Would Remove the Opportunity for Family Involvement in the "Death Drama"

Both those in favor of and those opposed to legislation establishing the concept of brain death espouse arguments based on family involvement. Those opposed say that such legislation would limit and reduce, if not eliminate, the family role in the death drama. if a doctor is compelled by statute to pronounce death upon establishment of brain death, they argue, the desirable role and rights of family could be precluded. Unfortunately, the critics of the legislation do not clearly specify which aspects of the family's role would be precluded or limited.

Once the question is properly phrased and understood as, "Is this person dead?", it is difficult to see what role the family has in reaching the answer to this question. The question calls for a "yes" or "no" answer. In other words, there are no medical alternatives which can be chosen by the family. The answer to the question is medically determinable, as is the determination that a person has lost a limb. The answer to this specific question does not, in any way, limit the options of the family in terms of burial, possible transplantation of organs, and other matters which must be attended to when a person dies.

On the other hand, enactment of brain death legislation would, we believe, go far toward alleviating many of the agonies of the family of a dying person. To prolong the determination and declaration of death beyond the actual time of death only extends the anguish of uncertainty and the suspension of life activity for the loved ones of the dead person. While uncertainty and interruption of routine living cannot be avoided, to prolong them beyond the point of death is cruelly insensitive to the needs of the surviving loved ones. In light of public uncertainty about death in the face of rapid medical advances, a legally sanctioned statement that a person is dead, when specified criteria are met, would partially alleviate anxiety and heartache by assuring the survivors that there is a firm legal basis for terminating artificial life support. Alleviation of emotional and psychological suffering is of primary importance. But alleviation of economic harm is also an important factor, and a statute would assist families not to feel obligated to continue expensive life supporting efforts once the loved one is in fact, dead.

Again, it is helpful to look at family involveme
from the point of view of the Quinlan and Elli
cases. Family involvment changes depending
each fact situation, and the interest of the f
changes throughout the dying process. Wh
family may still be involved in the dying proces
choose, this legislation prohibits them from
role in the medical determination of whether
occurred. In a situation such as that of Kar

where the individual is not brain dead, yet exists in a vegetative comatose state, the role of the family and its responsibility is greater than in a situation in which the person is brain dead. Family involvement and responsibility is greater in a Quinlan situation because the individual is alive, and the issue is the quality of that person's life. But, in an Ellison type situation, the individual is dead, and the family's involvement with the loved one as a living person ends. Once death occurs, the responsibility of the family is to care for the deceased body of the loved one and to deal with their own grief over the loss of the loved one.

The claim that the family should have some role in determining if their loved one is dead arises from a confusion between the questions, "Is this person dead?" and "Should this person be allowed to die?" Clear understanding of the difference between these questions should go a long way toward answering the concerns of opponents of brain death legislation.

The "Transplant" Argument is Not Based on Fact

The proponents of brain death legislation have openly argued that lack of a statute leads to a waste of potential vital organs for transplant to other, living persons. Opponents argue that this contention is not based upon fact, and that the Uniform Anatomical Gift Act,[21] which has been enacted in Minnesota, is sufficient to assure a supply of organs from those donors who are willing.

In our judgment, additional research is required to determine whether or not a brain death statute would result in an increase of transplantable organs. We doubt that it would, since current legislation permits removal of organs, with approval, from a person who would be brain dead under the brain death legislation. Thus, it would appear that a new statute would not affect this issue.

Opponents also argue, however, that life support systems are often terminated not because the person is dead, but because there is a need for the person's organs. In actual practice, this argument is unfounded because the Uniform Anatomical Gift Act requires that he physician involved in the transplant operation annot be involved in the determination of when death curs.

Brain Death Statute is the First Step Toward anasia

ponents of brain death legislation are obviously ned that any statute dealing with "life or death" may open the floodgates to the improper on of life. While we share their concern and this must not be permitted to occur, we do not believe the proposed brain death legislation does, in fact, carry such danger.

First, it must be remembered that even the opponents of this legislation agree that "brain death" is a perfectly acceptable standard of death; so if this definition of death will open the floodgates, then they have already been opened by the wide use of this medical standard and the opponents' concurrence in this practice.

Second, legislating the concept of brain death is *not* a step toward euthanasia since everyone agrees that it is to be applied to dead persons, not to living persons when deciding whether or not their lives should be allowed to end, as the proponents of passive euthanasia suggest, or to be terminated by medical intervention, as the proponents of active euthanasia suggest. It is not our purpose here to take up these controversial proposals, other than to point out as clearly as we can that they raise issues far different from those involved in the proposal to legislatively recognize the concept of brain death. Brain death is only a step toward euthanasia if we lack, now and in the future, the ability to keep straight the difference between the questions, "Is this person dead?" and "Should this person be allowed to die?"

Conclusion

Brain death legislation deals with the reality and inevitability of death once it has occurred. It provides a reliable indicator that, without question, human life has ended. Brain death deals not with uncertainty, but rather with the certainty that an identifiable event — death — has occurred.

We live in a world of uncertainties, many of them compounded by the enormous expansion of human technological control over the life process. We often question the meaning of our own lives, especially when we experience severe physical or mental illness in ourselves or a loved one. In these circumstances we may question whether such a debilitated existance is really living at all. These uncertainties about life and the qualities which make it worth living cannot easily be dealt with in the legislative or judicial processes. They are uncertainties with which each of us must ultimately deal, according to our own understanding of life.

In contrast to these uncertainties, doubt about the occurrence of death has been removed by modern technology which has given us the ability to determine that death has occurred, even though the heart and lungs may continue to function as the result of medical technological intervention. While such intervention is appropriate to give the dying person every chance of living, continuation of such intervention after the brain is irreversibly destroyed is a fruitless effort to deny the reality of death.

Acknowledgment

The authors gratefully acknowledge the contribution of Rebecca A. Knittle, J.D., who provided helpful critical comment and editorial assistance. The authors are solely responsible for the opinions expressed herein.

Footnotes

1. S.F. 253:

   > "A person shall be pronounced dead if, in the opinion of a physician, based on current standards of medical practice, that person has experienced an irreversible cessation of spontaneous respiratory and circulatory function. In the event that artificial means of support preclude the determination that these functions have ceased, that person shall be pronounced dead if, in the opinion of a physician, based on current standards of medical practice, that person has suffered irreversible cessation of clinically determined total brain function."

2. This legislation will be introduced and sponsored by Senator Jack Davies, who served on the Special Committee on Uniform Brain Death of the National Conference of Commissioners on Uniform State Laws.
3. The Board of Trustees of the Minnesota Medical Association endorsed the Uniform Brain Death Act on October 14, 1978.
4. For an excellent anthology of essays on these and related issues, see Death, Dying, and Euthanasia (D. Horan and D. Mall, 1977).
5. Black's Law Dictionary 488 (Revised 4th ed. 1968).
6. Cranford, Medical Aspects of Brain Death, Vol. 3, No. 10 Minnesota Trial Lawyer 3 (Sept. 1978).
7. On the dilemma this poses to physicians, see generally Collins, Considerations in Prolonging Life: A Dying and Recovery Score, in Death, Dying, and Euthanasia, (D. Horan and D. Mall eds. 1977), supra note 4, at 3.
8. Nineteen states had adopted some form of brain death legislation by December 1978 The leading article in this field, which has influenced much of the debate and subsequent legislation, is Capron and Kass, A Statutory Definition of the Standards for Determining Human Death: An Appraisal and a Proposal, 121 Univ. Pa. L. Rev. 87 (1972), reprinted in Death, Dying, and Euthanasia, supra note 4, at 40.
9. de la Rosa, Murder to be Charged, but Victim "Lives," Minneapolis Tribune, June 18, 1978, §A, at 1, col. 3; Cope, Death, Like Pregnancy, is an All-or-Nothing Thing, Minneapolis Tribune, June 22, 1978, §A, at 1, col. 1; Stone and Cope, Child's Heartbeat Stops After Respirator Removed, Minneapolis Tribune, June 12, 1978, §A, at 1, col. 6; Associated Press, Judge Agonized over Ruling to "Pull Plug," Minneapolis Tribune, July 19, 1978, §B, at 1, col. 2.
10. State v. Gerszewski, DC File No. 70261, CA File No. 78-0751 (Hennepin County, Minnesota, District Court July 29, 1978) (memorandum). In its memorandum opinion the court adopted the definition of "brain death" utilized in Commonwealth v. Golston, 366 N E. 2d 744, at 747-48 (Mass. 1977) which reads as follows:

    > . . . Brain death occurs when, in the opinion of a licensed physician, based on ordinary and accepted standards of medical practice, there has been a total and irreversible cessation of spontaneous brain functions and further attempts at resuscitation or continued supportive maintenance would not be successful in restoring such functions.

    Reliance upon this case by the court in the Ellison case is noted in Stone and Cope, supra note 9 at 5, cols. 3 and 4.
11. County of Hennepin v. Soderquist, DC File No. 747901 (Hennepin County, Minnesota, District Court July 18, 1978) (order and memorandum). See also Ex Parte Petition of Hennepin County, July 17, 1978, and Affidavit of Dr. Ronald E. Cranford, July 17, 1978 in the court file; and Kimball, Court Orders Respirator Shut Off, Minneapolis Tribune, July 20, 1978, §B, at 1, col. 5.
12. 70 N.J. 10, 355 A.2d 647 (1976).
13. Among the first criteria developed were those of the Harvard Medical School. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, A Definition of Irreversible Coma, 205 J.A.M.A. 338 (1968). The current Minnesota brain death criteria as developed by the Ad Hoc Committee on Death of the Minnesota Medical Association are quoted and discussed in Cranford, Brain Death: Concept and Criteria, 61 Minnesota Medicine 561 (Part I), Sept. 1978), 600 (Part II) (Oct. 1978).
14. Supra note 11.
15. Supra note 9.
16. Supra note 6
17. J. Market, Executive Director of the Minnesota Catholic Conference, Policy of Minnesota on Death: "Death Definition," (unpublished statement delivered to Senate Judiciary Committee of the Minnesota State Legislature, Feb. 28, 1977).
18. See, e.g., the memorandum decision, Supra note 10.
19. The Soderquist case, supra note 11, is a clear example. In that case no relatives of Hazel Soderquist were located. Normally courts appoint a guardian ad litem to represent the interests of an incompetent person. In Soderquist, however, the court undertook to proceed without appointing a guardian ad litem.
20. For a discussion of this unreported decision see Comment, Medical Malpractice — Determining the Time of Death of the Heart Transplant Donor, 51 No. Car. L. Rev. 172 (1972) and Capron and Kass, supra note 8 at 98-100.
21. Minn. Stat. § 525.927.

Natural Course of Rheumatoid Arthritis – Colton (page 130)

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Continuing Medical Education

Hospice Organization

Hospice — Developmental and Organization Concerns is the theme for a conference to be held at the Marriott Hotel, Bloomington, Minnesota, on March 2 and 3, 1979. This is a regional conference for the National Hospice Organization, and is locally sponsored by Hospice St. Paul, Bethesda Lutheran Medical Center, the Minnesota Chapter of the American Cancer Society, and the Coalition for Terminal Care. Registration fee is $50.00 and includes two lunches and a dinner. This program has been planned with careful consideration of regulations for contact hours for various professional organizations in Minnesota. Registration deadline is February 15th. For further information, contact:

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(Continued on Page 136)

Rheumatology Corner

Natural Course of Rheumatoid Arthritis

ROGER COLTON, M.D.*

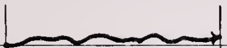
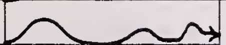
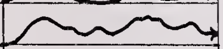
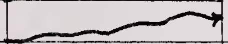
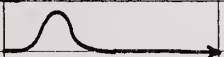
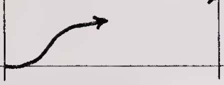
PROGNOSTICATING THE course of each rheumatoid arthritic's (RA's) disease can facilitate a judicious management program. Some 6.5 million Americans have rheumatoid arthritis and require medical care; a substantial number may have limited disease such that medical care is not sought or has been misdiagnosed. Long-term studies of a significant population of RAs reveal a benign course, and those with significant disease may find their disease remitting spontaneously. This article is a synopsis of accumulated literature to provide the physician with an overview of the disease and aid in prognosticating the course of RA.

Table 1 represents the time course of a monitored rheumatoid population. Twenty percent of RAs may spontaneously resolve their disease within the first year (Table 1, group E). A majority of the rheumatoid population have chronic, intermittently active low grade rheumatoid disease which may not come to medical attention, or if so, may be difficult to treat because of "minimal disease" or "nuisance disease" (Table 1, group A). The bulk of chronic RAs who regularly require management and follow up are those with active progressive disease with sporadic and usually brief remissions or reductions in their active disease states (Table 1, groups B, C, and D). The majority of these individuals may have productive lives, albeit with temporary setbacks associated with their disease. Observations of the natural course of rheumatoid arthritis in 300 patients followed over 16 years in the presurgical and limited drug formats of years past, showed 60% of patients independent (but 2/3 with minor disabilities), and 25% with handicaps necessitating work limitations.[1] This group, with the 15% who became incapacitated with active progressive disease today have more aggressive long-term therapy, available to significantly limit their disease.

A basic conservative program is reasonable in the first months of the disease because of the possibility, but unpredictability, of spontaneous remission. A profile of favorable compared with unfavorable signs and symptoms can be used to anticipate the course and extent of RA (Table 2). Signs and symptoms of increasing systemic joint involvement both in number of joints and intensity of disease, rising rheumatoid factor titer, and joint erosions by x-ray portend active progressive destructive disease less likely to remit. Therapeutic decisions can be predicated with hopes of influencing rheumatoid arthritis early in its pathophysiologic course. RAs who receive education and management programs early in the course of their disease with aggressive therapeutics as increasing synovitis is documented, are likely to be spared or minimized possible disability. Further articles will address basic and aggressive treatment programs for rheumatoid arthritis. Advancing from a

TABLE 1*

Natural Course of Rheumatoid Arthritis

Group	Course	% of the Rheumatoid Population	Comment
A		50%	"Smoldering" low grade sporadically active RA
B		25%	Chronic, active, summarily progressive RA, likely destructive joint disease with extra-articular manifestations
C			
D			
E		20%	Complete remission with or without therapy over one year
F		5%	Fulminant RA -- active progressive unrelenting

[1] modified from Short et al.

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*St. Paul, Minnesota.

basic program to the addition of suppressive drugs implies that the alert physician anticipates ongoing disease.

Young adult females to middle-aged patient population have been considered the bulk of rheumatoid population. However, a quarter million children have rheumatoid disease and their general course and prognosis have also been charted according to their presentations (Table 3). Data for the course of arthritis in senior citizens is limited, but rheumatoid disease started at an older age, particularly in males, tends to be more aggressive and warrants consideration of early aggressive therapy.

The half billion dollar arthritic quackery industry takes advantage of the lack of predictability of the natural course of the disease. Hence, using copper bracelets, immune milk, alfalfa, mega doses of vitamins, cod liver oil, fad diets, etc. can appear to help the sporadic course of RA, which after significant active disease may be in a prodromal phase of spontaneous remission when "treatment" is instituted. It behooves physicians to discuss the natural course of the disease (with generally good prognosis) with their patients for understanding and cooperation in appropriate management programs while being made aware of the illusions of quackery.

TABLE 2*

Prognostic Factors in Rheumatoid Arthritis

Favorable		Unfavorable
Under 40	AGE	Over 60
Female	SEX	Male
Acute, large joints — oligoarticular	ONSET	Indolent, symmetrical small peripheral joints
Less than one year	DURATION	Chronic
	PHYSICAL SIGNS	
absent	— nodules	More likely to develop
absent	— cutaneous vasculitis	More likely to develop
negative	— x rays	'porosis, loss of joint space, erosions
	LAB	
"Low"	sed. rate	high — often 80 to 110
negative	RH factor	positive in high titer
less likely	Anemia	likely, with eosinophilia
unlikely	Other antibodies (ANA, Sjogren's)	likely

*modified from Short et al.

TABLE 3*

Patterns of Juvenile Rheumatoid Arthritis

Types	Course of Arthritis
I. Systemic onset (Still's Disease)	Severe in 25%
II. Multiple joints, RF –	Severe in 15%
III. Multiple joints, RF +	Severe in 50%
IV. Few joints, RF –	"Mild" disease

(RF + = rheumatoid factor +)
(RF – = rheumatoid factor –)

*modified from Schaller

References will be found on page 127

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apeutically, (as an adjunct to sys- dicated), for topical infections, ue to susceptible organisms, as rafts, surgical incisions, otitis as (impetigo, ecthyma, ia); secondarily infected es, and seborrheic derma- med or suppurating as a *rophylactically*, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components. Do not use in the eyes or in the external ear canal if the eardrum is perforated.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chro dermatoses, it should be born mind that the skin is more liable to bec sensitized to many substances, including neomyc The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as fa to heal. During long-term use of neomycin-contai products, periodic examination for such signs is advisable and the patient should be told to discon the product if they are observed. These symptom regress quickly on withdrawing the medication. Neomycin-containing applications should be avoi for that patient thereafter.

PRECAUTIONS: As with other antibacterial prep tions, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occu

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reporte (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

Minnesota Medical Association

Syllabus

A compendium or summary outline of a discourse, treatise, course of study or examination requirements; a series of abstracts. (Webster)

Recognition and Care of the High Risk Pregnant Patient and Neonate

The educational objective of this 6-hour course was to further enlighten those physicians involved with obstetrics and newborn care relative to the management of the high-risk pregnant patient and the distressed neonate. The course was divided into two parts. The obstetric aspect included the identification of the truly high-risk patient, the clinical and newer laboratory modalities available for the critical assessment of the pregnancy, and the intrapartum management of the high-risk situation. The neonatal section outlined the care of the asphyxiated neonate, the early recognition of the more subtle problem neonates, and considerations for stabilization of the sick neonate and transport when necessary.

Jack L. Strobel, M.D.*
Moderator

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*Minneapolis.

The Management of Labor in the High-Risk Patient

RICHARD P. BENDEL, M.D.*

The first decision in the high-risk pregnancy is whether or not to allow labor at all. This decision can now be made more competently by thoughtful use of the non-stress testing, OCTs and estriols. Despite these antepartum tests, there are certain situations in which labor should not be induced or if spontaneous labor begins, the patient should be sectioned immediately. Some of these are as follows:

Breech — The author believes that the breech presentation baby should be delivered vaginally only if all other factors are normal. If a high-risk patient for other causes, i.e. severe preeclampsia, IUGR, etc., also has a breech, then straight off cesarean section. Fetuses from 28 weeks to 34 weeks also should be sectioned. These small prematures now have an excellent chance in a good NBICU — if they are not damaged during labor and delivery.

Erythroblastosis — If excess O.D. is in Zone III on Liley's graph, i.e. you expect cord hemoglobin to be less than 8 gms.%, than cesarean.

Abruptio placentae — If the fetus is alive, then cesarean.

There are many other high-risk pregnancies in which the cesarean section rate will be very high, but labor with vaginal delivery expected would be the usual initial management.

The ideal management of labor in the high-risk patient involves the following four capabilities.

1. A complete understanding of the normal course and progress of the stages of labor.
2. Availability and experience with electronic fetal monitoring and fetal scalp pH.
3. Readily available anesthesia and cesarean section.
4. Newborn intensive care unit.

Let's take these four points in order. In the discussion of point one, most of my recommendations are based on the writings of E.A. Friedman, M.D.[1] Although many individual labors vary from the patterns described by the Friedman curves, by and large they hold true for the majority of patients.

The first problem we encounter is the prolonged latent phase of labor. It is a specific, common an *innocuous* pattern. The latent phase may last up to hours in the nullipara and 20 hours in the multipa During this time, cervical dilatation is less than 3 and 4 cm. respectively, and the contraction usually somewhat irregular in quality and interv etiology appears to be secondary to onset of la an unfavorable cervix and excessive medicat treatment for a long latent phase of the fir labor is therapeutic rest and expectanc up studies indicate that fetal and newborn outlook is not made worse by a prolonged latent phase.

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*Hennepin County Medical Center, Minneapolis, Minnesota.

Then we come to disorders of the active phase of the first stage of labor. After the nullipara has readied 3 cm., she should progress with cervical dilation of at least 1.2 cm./hr. The multipara should progress at 1.5 cm./hr. cervical dilation. Arrest is defined as failure to progress over a two-hour period. Fifty percent of these are due to cephalopelvic disproportion (CPD) and require cesarean section. In the high-risk patient, if you do not have electronic monitoring available, then cesarean section is indicated for arrest of progress.

Finally, there is failure of descent of the presenting part. Descent should begin in the last part of the first stage of labor, i.e. when the cervix is 8-9 cm. and progress at a rate of 1 cm./hr. in the nullipara and 2 cm./hr. in the multipara. If an arrest develops, get x-ray pelvimetry, and if no disproportion, careful oxytocin stimulation may be tried. If you are not completely equipped to monitor the patient or if there is already some degree of uteroplacental insufficiency, then immediate cesarean section.

Electronic fetal monitoring has become standard in following high-risk patients during labor and vaginal delivery. Although there are some physicians who still question the efficacy of monitoring in the apparent normal parturient, nearly everyone agrees that high-risk patients should be electronically monitored. At USC-LA County, in more than 10,000 high-risk patients, their intrapartum fetal death rate has been cut to nearly zero by monitoring. They have had more intrapartum fetal deaths in their "normal patients" who have not been monitored.

The most ominous patterns in fetal heart rate tracings during labor are: (1) Repeated late decelerations. (2) Repeated severe variables (drop of 60 beats per minute and lasts for 60 seconds or longer). and (3) Loss of baseline variability, i.e. flat baseline, especially if associated with deep variables.

When any of these develop, immediate measures must be taken. These include changing the position of the mother, administering O_2 by mask at 7-8 l/min., topping oxytocin, and doing a vaginal exam to rule t prolapsed cord and assess dilatation of the cervix, tion of presenting part, etc. If scalp pH is available, it should be obtained. If not available, and these ns persist for up to 30 minutes, then immediate cesarean section is indicated.

Many fetal heart rate tracings are a mixture of decelerations and strips of more normal looking patterns. It is in these labors that fetal scalp pH is most beneficial. If the scalp pH is greater than 7.25, then fetus is not in jeopardy. If pH between 7.20 and 7.25, then repeat in 30 minutes or sooner depending on evolution of FHR tracing. If pH below 7.20, then prepare for immediate cesarean and do another scalp pH immediately so it can be run during the preparation for cesarean. If still below 7.20, then cesarean.

The third category is cesarean section and anesthesia. Units taking care of high-risk patients should be able to set up and do a cesarean section within 15 minutes.

The best anesthesia for cesarean section for fetal distress is balanced general anesthesia with pentothal induction. All patients should be given 2 oz. of liquid antacid before cesarean to prevent the serious pneumonitis associated with the aspiration of acid-peptic juice. If your anesthesiologist won't cooperate and insists on spinal or epidural, then be sure that patient is well hydrated and table titled maximally to minimize hypotension.

Finally, a few words about having the NBICU in the same facility as labor and delivery. As an obstetrician, there is no better feeling, in my estimation, then being able to hand over a tiny or compromised newborn directly to the neonatologist. It stands to reason that if the infant can be intubated, ventilated, kept warm and needs only to be transported across the hall to the NBICU, you have the ideal situation. In some situations it makes the difference in whether the newborn lives or dies. For example, we have saved an erythroblastotic infant with hydrops and a cord hemoglobin of 2 gms.% — by immediate transfusion and supportive measures in the delivery room. If the tiny premature can get immediate expert ventilation, acidosis can be prevented, thereby decreasing intracranial bleeding and improving survival. Another advantage of the perinatal center concept is improved communications between obstetrician and pediatrician. Rounds on high-risk mothers can be made jointly, problem discussed and timing of delivery sometimes adjusted for optimal preparations and use of personnel and equipment.

Reference

1 Friedman, EA: Patterns of labor as indicators of risk. Clin Obstet Gynecol 16:172, 1973.

Prenatal Detection of Genetic Diseases

RICHARD P. BENDEL, M.D.

Prenatal detection began about ten years ago and has now become an established procedure. At Hennepin County Medical Center and the University of Minnesota, we are now seeing three or four patients each week for genetic amniocentesis. However, we estimate that at least five times as many patients in Minnesota each year would be eligible for these procedures. Courts in some states have now ruled that a physician is negligent if she/he does not inform the high risk patients of the availability of these services.

Who Is At Risk?

A. Women 35 and older. Chromosomal disorders increase in frequency with advancing maternal age. See adjacent TABLES I and II. The overall incidence of Down's Syndrome is one in 600 births, but a 20 year old mother has only one chance in 2,000 of having a mongol, while a 45 year old mother has one chance in 25 of having an affected child.

TABLE I

Maternal Age	Chance of Trisomy 21 (Mongol)
20 y/o	1 in 2000
30	1 in 1000
35	1 in 300
40	1 in 100
45	1 in 25

TABLE II

Maternal Age	Chance of Detectable Disorder
35-39	1½-2%
40-44	4-5%

B. Previous Trisomy.
A woman has previously delivered a child with Down's Syndrome has an increased risk of another child with the disorder. Her risk of recurrence is between 1-2%.

C. Balanced Translocation Carriers.
Individuals who are balanced carriers, while normal themselves, have a high risk of having an affected child — as high as 50%, depending on the type of translocation.

D. X-Linked Recessive.
Mothers who are carriers for such diseases as Duchenne's Muscular Dystrophy and hemophilia (Factor VIII deficiency) pass the disease on to their male offspring. 50% of the males will be affected. The sex of the fetus can be determined and in some cases, such as Lesch-Nyhan, the affected males can be detected.

E. Metabolic Errors.
Approximately 100 inborn errors of metabolism can now be diagnosed prenatally. Most of these are autosomal recessives so that both parents are carriers and they have a 25% chance of an affected child. Some of the more common disorders are Tay Sachs, Fabry's, Niemann-Pick, Krabbe's, etc.

F. Neural Tube Defects (NTD).
In open neural tube defects, alpha-fetoprotein levels in amniotic fluid are elevated above normal. The inheritance is thought to be polygenic and perhaps environmental, and a couple who has had one child with a NTD has a 4% chance of another. If they have two children with NTD, then their risk for recurrence is 12%.

Procedure and Risks

The amniocentesis is done at 15-16 weeks menstrual age (13-14 weeks from conception). At that stage of pregnancy, the amniotic fluid volume is about 150-200 ml.

Ultrasound is done at the time to measure fetal biparietal, localize placenta and rule out twins. (The author interprets his own sonograms and does the "amnio" right in the ultrasound room.)

There is essentially no risk to the mother from amniocentesis.

There is a 0.5-1.0% risk of the pregnancy aborting in the month following the amniocentesis.

Direct injury to the fetus is a very rare occurrence. If it does occur, it most likely results in fetal death and abortion. There are 7 or 8 case reports of a minor "dimple" or linear scar found on a newborn, following genetic amniocentesis.

If the mother is Rh negative, and the fetus Rh positive, there is a slight risk of isoimmunization. In these cases, Rh immune globulin may be given.

The laboratory is successful in culturing the amniotic fluid cells 97% of the time.

It takes three to four weeks to culture the cells and study the karyotype.

The chromosomal studies have proven to be 99.7% accurate in collected series.

The total cost is currently about $400.00. Includes ultrasound, amniocentesis, cell culture and karyotype, and alpha-fetoprotein measurement.

It is not expected that everyone doing obstetrics can be an expert on genetics. However, expert consultation is as close as your telephone and below are listed the names of some people who can help you with your questions.

Richard P. Bendel, M.D., Assistant Chief
Department of Obstetrics-Gynecology
Hennepin County Medical Center
(612) 347-2750

Robert Gorlin, D.D.S., Professor and Chairman
Oral Path
University of Minnesota
(612) 373-3248

Dight Institute for Human Genetics
University of Minnesota
(612) 373-3792

Richard A. King, M.D., Associate Professor
Medical & Human & Oral Genetics
University of Minnesota
(612) 373-4999

Gregory A. Grabowski, M.D., Pediatric Genetics Fellow
University of Minnesota
(612) 373-4529

(Continued from page 128)

THE FARIBAULT CLINIC, LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

12 PHYSICIAN, multi-specialty clinic needs an Ob-Gyn. Ours recently retired. The present group includes general surgeons, internists, a urologist, an ophthalmologist, an otolaryngologist and family practitioners. Northeastern Minnesota location with complete hospital facilities. Excellent recreation country, both summer and winter. Solid and growing economic conditions. No big city problems. Please call collect relative to any questions. Reply — Mesaba Clinic, Hibbing, MN 55746 or call John Brust at (218) 262-3441.

THREE YEAR APPROVED Psychiatric Residency Program now appointing for an immediate unexpected opening and for July, 1979. Small intensive psychiatric hospital, JCAH approved, affiliated with University of Iowa Medical College. Comprehensive program including two adult psychiatric units, adolescent unit, childrens unit, alcohol & drug abuse unit, with innovative community liaison, and OPD. Eclectic approach. Situated in picturesque northeast Iowa near large cities with cultural advantages, but in rural setting. Ideal for family living. No financial sacrifice while learning. Top salary: first year $23,478, second year $24,648, third year $25,896; liberal fringe benefits; some housing available. Opportunity to join staff upon completion of training. All applicants must have completed one year in an American approved training program in internal medicine, family practice, or pediatrics or a flexible one year program, including four months in internal medicine. Wirte or call J. T. May, M.D., Superintendent, or B. J. Dave, M.D., Director of Education, Mental Health Institute, Independence, Iowa 50644.

FAMILY PRACTITIONER — Internist — 14 man mixed Family Practice Speciality Group with a modern clinic wishes to add an additional Family Practitioner and Internal Medicine Doctor. Have one satellite office. Modern hospital one block from Clinic. Desirable community with excellent school system. Good salary and wide range of fringe benefits. Contact Thomas A. Treanor, M.D., Albert Lea Medical and Surgical Center, Ltd., Albert Lea, Minnesota, Phone 373-1441 or 373-3051.

PSYCHIATRIC RESIDENCY: Immediate vacancies for PG2 through PG4 through July 1, 1979. Those eligible for an Iowa Residents license via the ECFMG receive stipends of: 1st year, $21,294; 2nd year, $22,360; 3rd year, $23,478. Those eligible for a regular Iowa license vie FLEX or reciprocity receive stipends of: 1st year, $23,478; 2nd year, $24,648; 3rd year, $25,896. T. B. McManus, M.D., Superintendent, Mental Health Institute, Cherokee, Iowa 51012. Call Collect 712-225-2594. Equal Opportunity Employer.

WANTED: PSYCHIATRIST for Mental Health Center and/or private practice Northwest corner of state. Center desires additional psychiatrist in area. Will either guarantee development of private practice, or full time position with the Center of combination. Excellent salary and fringe benefits. Delightful professional staff developing innovative programs in the seven county area. A professionally exciting opportunity. Contact Roy Waters, Executive Director, Northwestern Mental Health Center, College Avenue, Crookston, MN 56716. Phone: area code (218) 281-3940

SUBURBAN MINNEAPOLIS: Opening in early 1979. 3-man Family Practice Group (PA) is looking for a replacement for a member entering the teaching field. Salary and Bonuses. Own lab & X-ray, 600-bed hospital with complete facilities and consulting staff a few blocks away. Call collect — or write to: Robbinsdale Clinic, PA, 3819 West Broadway, Robbinsdale, Minn. 55422. ATTN: Donald D. Metz, M.D. (612) 533-2534.

15 DOCTOR MULTISPECIALTY group is looking to add two doctors in the Family Practice Dept.; one doctor in orthopedic surgery, internal medicine and OB/GYN. Recreational, educational and cultural opportunities abound in small town atmosphere of northern Minnesota. New clinic and hospital under construction. Contact D. E. Carlson, Bemidji Clinic, Bemidji, MN 218-751-1280

(Continued to Page 138)

Farewell Old QACME

"O frabjous day! Callooh! Callay!"

— Carroll

During 1978 QACME has tried to answer your CME questions and prepare all licensed beamish boys to slay the licensure Jabberwock in 1979. The day of reporting is here and QACME'S usefulness has waned. But, QACME also has to submit a report and this is how he plans to do it.

QACME's birthday is January 6 and thus belongs to MSBME Class I (50 hours of CME required by 1, January 1979). As a vorpal pencil is sharpened to snicker-snack the form sent by the Minnesota State Board of Medical examiners:

I KNOW — the form will contain my name, licensure number, address, birthdate, age, sex, the HOURS claimed for Categories I-V (not the details) and my signature attesting the accuracy of the report.

I KNOW — the Board may later ask documentation of the claimed hours of CME, so my faithful secretary will file the supporting material including, 1) the sponsoring organization, 2) the program of meeting (or description of course and time of attendance), 3) the location and name of facility where the program was conducted and 4) the names and credentials of the presentors (such as may be found in the program).

I SHALL — list under Category I only the total hours of my attendance during 1978 at Minnesota Medical Association's Scientific Assembly, American College of Surgeons, A.M.A., Minnesota Surgical Society, Central Association of Obstetricians and Gynecologists, Mayo Clinical Review, University of Minnesota Surgical Review, Mayo Clinic Grand Rounds and Chief Resident Conferences and some, but not all; presentations that are part of my Departmental weekly and biweekly conferences. (These will be more than the required 20 hours.)

I SHALL — place under Category II the total hours of attendance at the Muncie Academy of Medicine, the American Group Practice Association, many of my hospital and clinic weekly staff meetings. (There will be more than 15 hours this year, but I shall only put down "15" as that is the limit.)

I SHALL — place under Category III the total hours of my teaching of medical students, residents, physicians and allied health professionals. With residents, medical school students and clerks regularly assigned to my hospital service, this will be easy. (However, I shall put down 15 hours only because that is the limit for 1 year.)

I SHALL — place under Category IV the total hours of my formal presentations — papers read (10 hours each), papers published (10 hours each) and completed medical documents designed for institutional or professional use, but not necessarily for publication. (I shall list only the limit of 13 hours, although my secretary will probably put down 15 hours. It won't matter though because there are plenty more.)

I SHALL — place under Category V the total hours of my personal reading appropriate to my medical activities — texts, periodicals, special reviews, basic science studies. I don't serve on a peer review or audit group, I took SESAP II in 1977 and I'm not yet eligible for recertification — but there's enough without those. (I shall list only the limit of 15 hours, but my secretary will file a more detailed estimate time of Category V.)

Now that my "vorpal blade" has gone snicker-snack and I have left the Jaberwock dead, I can chortle "Oh frabjous day! Callooh! Callay!" However, I shall read all documents carefully once again, sign legibly where indicated, make copies for my licensure file, complete the reregistration application, enclose a check, address and stamp the envelope and mail promptly to the Minnesota State Board of Medical Examiners, 717 Delaware Street S.E., Minneapolis, Minnesota 55414.

I SHALL — NOT mail to Minnesota Medical Association!

MINNESOTA MEDICINE and MMA will always be available to answer CME questions. However, old QACME grows mouldy, and with thoughts of breeding the past once again, he really should be put away. Let us do so with this letter! With apologies to Shakespeare, we might now end QACME with:

Goodnight, sweet QACME,
And flights of properly
Completed CME forms, Thee,
Sing to thy rest.

J.S. Welch, M.D.
for the
Medical Education Committee
Minnesota Medical Association

(Continued from Page 136)

INTERNAL MEDICINE, FAMILY PRACTITIONER OB-GYN AND PEDIATRICIAN to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities; starting salary $40,000 to $50,000 per year. Contact Personnel Director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611.

WANTED— M.D. or D.O./FAMILY PRACTICE to join gr. of 3 FP/MD's. Exc. new clinic attached to 120 bed hosp. Full hosp. priv. avail. Salary 1st yr. then may join corp. Thriving comm. of 10,000 + with lg. drawing area. Fine recreational and social area with first class school system & all churches avail. Easy freeway access to metro area. Contact Family Clinic, 808 3rd St. S.E., Little Falls, MN 56345 or call collect D. R. Seifert M.D. (days) 1-612-632-2301, (evenings) 1-612-632-9150.

ORTHOPEDIC SURGEON Board Certified Orthopedist has need for associate to join a 14 man multispecialty group with modern fully equipped facility across street from 200 bed general hospital and rehabilitation center. Hospital has recently completed a 6 million dollar remodeling and modernization project. Medical catchment area of 100,000. Located in a small, friendly city of 13,000 with excellent schools, recreational areas. Interested applicants should call or write: Jay A. Davenport, M.D. or Harlan A. Hillmer, Administrator, Lenont-Peterson Clinic, Ltd., 820 North 9th Street, Virginia, Minnesota 55792. Phone: (218) 741-4292.

INTERNIST AND 2 FAMILY Practitioners to join the Coon Rapids Clinic, with a staff of 9 family practitioners, 2 pediatricians, 3 obstetricians/gynecologists, and 1 general surgeon. For more information contact Mark H. Brakke, M.D., or James Sipe, M.D. at the Coon Rapids Clinic, P.A., 9920 Zilla Street N.W., Coon Rapids, Minnesota, 1 (612) 755-1621.

NATIONWIDE AND EUROPE — Army seeking physicians to age 58. Salary from $33,000 depending on qualifications and experience. Choose your location. Relocation cost paid. Up to 30 days paid vacation yearly, no malpractice premium, excellent benefits. Type of practice, location, salary and rank guaranteed prior to two year obligation. GME available. CPT David James, US Army Medical Department, 180 E. Kellogg Blvd., Room 1526, St. Paul, MN 55101, (612) 221-9011.

ORTHOPEDIC SURGEON and Internist for multispecialty group with a Family Practice Department, Crookston, Minnesota. Located in heart of the Red River Valley, stable economy, good income, new clinic facility, full member in one year. Contact R. F. Schnabel, M.D., (218) 281-3184, Crookston, Minnesota.

WANTED: Internist for multi-specialty group in Detroit Lakes, Minnesota. Current multi-specialty group consists of seven family practitioners, three general surgeons, two internists, one obstetrician, two pathologists, and a radiologist. Physician-owned four-year-old clinic attached to a 100-bed hospital. First year salary with full participation in ownership negotiable at the end of one year. Fifty miles east of Fargo-Moorhead, in the Heart of the Lakes country. The area offers excellent recreational activities, with a top school system. Contact James F. Knapp, M.D. or John R. Emery, M.D. at Box 727, Detroit Lakes, MN 56501, or telephone (218) 847-3181.

EXPERIENCED FAMILY PHYSICIANS wanted to join clinic located in a suburb of Minneapolis, Minnesota. Please send inquiries and resume to Box 541, Minnesota Medicine, 101 E. 5th St., St. Paul 55101. The replies should be sent to my attention.

UROLOGIST: (Board certified or eligible) wanted to do Locum Tenens for one or two months. Willing to pay excellent salary for the coverage. Contact 218-681-6110, Thief River Falls, Minn. 56701. Retta Kotok for more information.

OPHTHALMOLOGIST WANTED IN SOUTHERN MINNESOTA Group Practice. The Albert Lea Clinic, P.A., in Albert Lea, Minnesota, a 16 man multi-specialty group is seeking a replacement for a senior man. Board certified or Board eligible. Salary guaranteed first year. Second year, participant in clinic's incentive income distribution plan. Low cost buy-in arrangement. Profit sharing plan. Top insurance plan with full range of other benefits. New hospital in city. A choice practice and exceptional place to live. Contact William Brouwer, Assistant Administrator, Albert Lea Clinic, P.A., 1602 Fountain Street, Albert Lea, Minnesota 56007, phone 507-373-8251, personal phone 507-889-6381 or contact Gary A. Boeke, M.D., 507-373-8251, personal phone 507-826-3288.

(Continued on Page 140)

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(Continued from Page 138)

WANTED: GP to join two GP's in practice in rural community northern Minnesota. Mod. clinic bldg. with good x-ray and lab. 40-bed hosp. new nursing home. Also need locum tenens for summer vacation time. Contact W.A. Pinsonneault, MD at Warren Clinic, Box 107, Warren, MN 56762 (218) 745-4151.

FOR SALE BY OWNER St. Croix valley home. Prestigious turn of century house in exclusive neighborhood. Sweeping river view. Thirty-five minutes from downtown Mpls. Phone 439-3183 after 6 p.m. or weekends.

OBSTETRICIAN-GYNECOLOGIST, to join 11 member primary care group. 7 Family Physicians, 2 Internists and 2 General Surgeons. Large patient population, newly remodeled and expanded Clinic facility approximately 6 blocks from modern, well equipped 99 bed hospital. Rural community 45 minutes South of the Metro area on 35W. Salary guarantee first year. For more information please contact: Darral Mischke, Clinic Administrator, Faribault Clinic, Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

INTERNIST Four Board Certified Internists have need for associate to join a 14 man multispecialty group with modern fully equipped facility across street from 200 bed general hospital and rehabilitation center. Hospital has recently completed 6 million dollar remodeling and modernization project. Medical catchment area of 100,000. Located in a small, friendly city of 13,000 with excellent schools, recreational areas. Interested applicants should call or write: Robert A. Nelimark, M.D. or Harlan A. Hillmer, Administrator, Lenont-Peterson Clinic, Ltd., 820 North Ninth Street, Virginia, Minnesota 55792. Phone: (218) 741-4292.

OB-GYN — Leading Twin Cities Clinic has immediate opening for board certified or eligible OB-GYN. Excellent benefits with first year salary to $60,000. Contact Timothy Holmes, 7250 France Avenue South, Edina, 55435, or call 831-5232.

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"Why Don't They Tell The Truth About Old Age?", George Sheehan, M.D., Redbank, New Jersey — cardiologist, Best-selling author, columnist, marathon runner.

ore prescribing, please consult complete product information, a nmary of which follows:

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rnings: As with most CNS-acting drugs, caution against hazardous occations requiring complete mental alertness (*e.g.*, operating machinery, ing). Withdrawal symptoms (similar to those with barbiturates, alcohol) e occurred following abrupt discontinuance (convulsions, tremor, lominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of disposition to habituation/dependence.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

L: Advise patients against simultaneous ingestion of alcohol and other S depressants.

of value in treatment of psychotic patients; should not be employed in of appropriate treatment. When using oral form adjunctively in convul- disorders, possibility of increase in frequency and/or severity of grand seizures may require increase in dosage of standard anticonvulsant dication; abrupt withdrawal in such cases may be associated with temary increase in frequency and/or severity of seizures.

ECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local tion, swelling, and, rarely, vascular impairment when used I.V.: inject vly, taking at least one minute for each 5 mg (1 ml) given; do not use ll veins,* i.e., *dorsum of hand* or *wrist; use extreme care to avoid intrarial administration* or *extravasation. Do not mix* or *dilute Valium with* er *solutions* or *drugs in syringe* or *infusion flask. If it is not feasible to ninister Valium directly I.V., it may be injected slowly through the infusion ng* as *close* as *possible to the vein insertion.*

ninister with extreme care to elderly, very ill, those with limited pulmoy reserve because of possibility of apnea and/or cardiac arrest; connitant use of barbiturates, alcohol or other CNS depressants increases oression with increased risk of apnea; have resuscitative facilities availe. When used with narcotic analgesic eliminate or reduce narcotic dos- at least 1/3, administer in small increments. Should not be administered patients in shock, coma, acute alcoholic intoxication with depression of l signs.

s precipitated tonic status epilepticus in patients treated for petit mal tus or petit mal variant status.

hdrawal symptoms (similar to those with barbiturates, alcohol) have ocred following abrupt discontinuance (convulsions, tremor, abdominal/ scle cramps, vomiting, sweating). Keep addiction-prone individuals der careful surveillance because of predisposition to habituation/ pendence. Not recommended for OB use.

cacy/safety not established in neonates (age 30 days or less); proged CNS depression observed. In children, give slowly (up to 0.25 /kg over 3 minutes) to avoid apnea or prolonged somnolence; can be eated after 15 to 30 minutes. If no relief after third administration, propriate adjunctive therapy is recommended.

ecautions: If combined with other psychotropics or anticonvulsants, efully consider individual pharmacologic effects—particularly with known npounds which may potentiate action of Valium (diazepam), *i.e.*, enothiazines, narcotics, barbiturates, MAO inhibitors and antidepresnts. Protective measures indicated in highly anxious patients with acmpanying depression who may have suicidal tendencies. Observe usual ecautions in impaired hepatic function; avoid accumulation in patients h compromised kidney function. Limit oral dosage to smallest effective nount in elderly and debilitated to preclude ataxia or oversedation (inily 2 to 2½ mg once or twice daily, increasing gradually as needed or erated).

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg, bottles of 100 and 500; Tel-E-Dose® (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10, Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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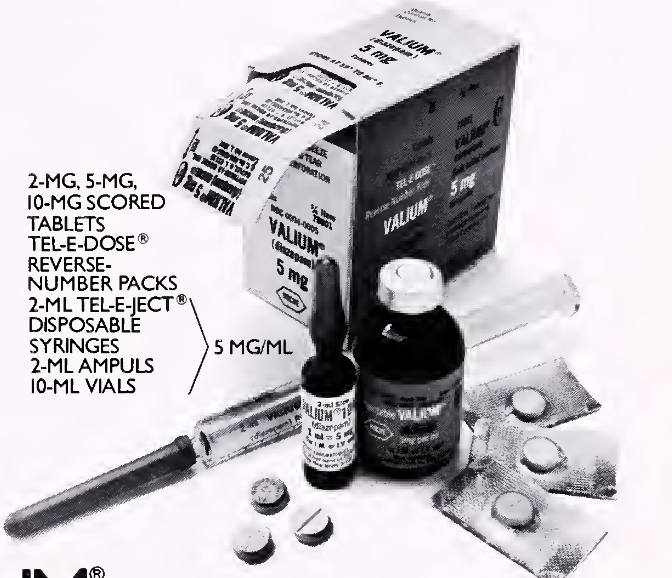

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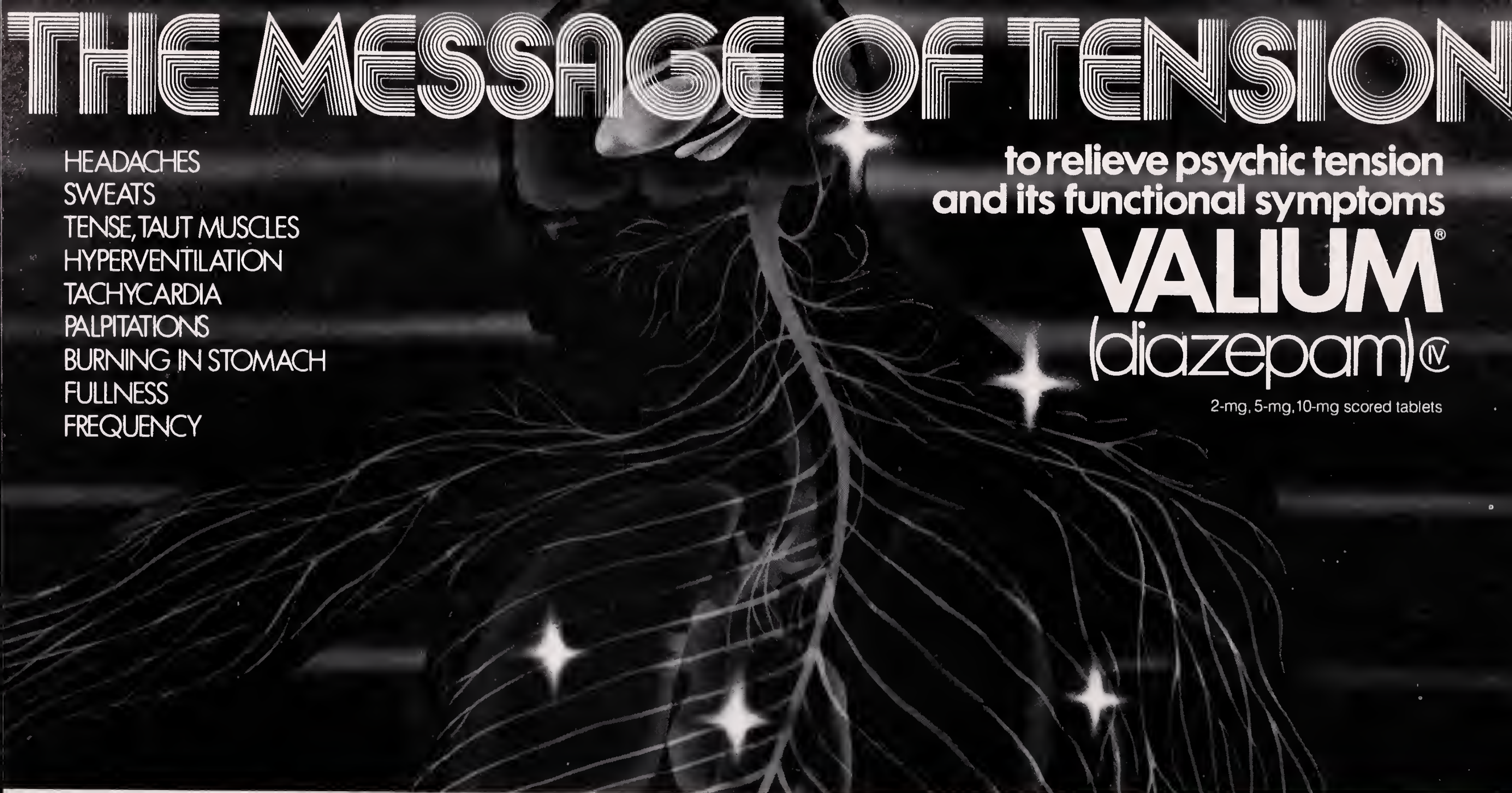
"Early Spring in Minnesota" *Carl Kjellstrand, M.D.*

MARCH 1979

Section 1 of Two Sections

THE MESSAGE OF TENSION



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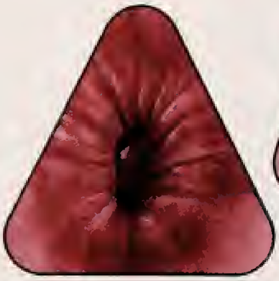

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Contents — March, 1979

OVER PHOTOGRAPH — "Early Spring in Minnesota"
Carl Kjellstrand, M.D. 161

RESIDENT'S LETTER — MMA is Constantly Working for Us
Robert S. Flom, M.D.
President, Minnesota Medical Association 145

DITOR'S NOTEBOOK — Postcards from Dubrovnik, London, and Lonsdale
Richard L. Reece, M.D.
Editor-in-Chief 147

RIGINAL CONTRIBUTIONS

Traumatic Atlantocranial Dislocation with Survival
Gaylan L. Rockswold, M.D. and Edward L. Seljeskog, M.D. 151
Enucleating Donor Eyes and Uses of Donor Eyes
Ronald Linde, M.D. 153
Skiing Injuries to the Urinary Tract
T.A. Hildreth, M.D. et al 155
Cadaver Kidney Transplantation — Effect of Hypotension and Donor Pretreatment with Methylprednisolone and Phenoxybenzamine
Luis H. Toledo-Pereyra, M.D. et al 159

ABORATORY LETTER — The Laboratory Evaluation of Thyroid Function
Michael W. Steffes, M.D. and Jack H. Oppenheimer, M.D. 162

MERITUS EDITOR'S SOLILOQUY — We'll See You in A Moment
Carl O. Rice, M.D., Editor Emeritus 188

DITORIALS

Colonoscopic Polypectomy and Beyond
Frederic D. Nemer, M.D. 171
RH Isoimmunization — *Hreidar Agustsson, M.D.* 175
Urologic Ski Injuries — *Gordon W. Strom, M.D.* 175

ENERAL MANAGEMENT GUIDELINE FOR THE ALCOHOLIC AND THER CHEMICALLY DEPENDENT
Thomas G. Briggs, M.D. 176

SPECIAL ARTICLE — RH Isoimmunization Prevention Program in a Community Hospital
Arthur C. Aufderheide, M.D. 181

RHEUMATOLOGY CORNER — Diagnosis of Rheumatoid Arthritis
James Reinertsen, M.D. 185

FRACTURE CONFERENCE — Snowmobile Injuries in Children
Hamlet A. Peterson, M.D. et al 193

REVIEW — Experience with Colonoscopic Polypectomy — Review of 700 Polyps
Santhat Nivatvongs, M.D. and Stanley M. Goldberg, M.D. 197

MINNESOTA CERVICAL CANCER MORTALITY STUDY
Peter E. Fehr, M.D. et al .... Supplement I

MINNESOTA MEDICAL ASSOCIATION — Syllabus

Asphyxia and Resuscitation —
Roderick Krueger, M.D. 201
Annual Meeting
S. V. Thorson, M.D., Chairman
MMA Subcommittee on Scientific Assembly 156

CONTINUING MEDICAL EDUCATION 164, 172, 177, 183, 187, 196, 205, 210

CLASSIFIED ADVERTISING 206

INDEX TO ADVERTISERS 178

Volume 62:3
Pages 141-210

MINNESOTA MEDICINE REPRESENTS

- Association of Neurologists of Minnesota
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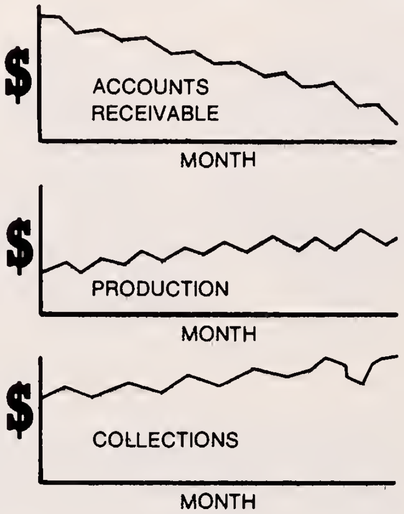

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President's Letter

MMA is Constantly Working for Us

In the course of trying to deal with ever increasing regulations by government agencies, MMA, its members, and its leadership have experienced many frustrations. Equally distressing to leadership and staff is the feeling that some members have felt their organization has failed them.

Whenever unwanted regulations finally come into our every day world, your MMA has been ever alert and active in these problems. But too often the successes have really not been visible, because they have been in the form of deleting an especially objectionable regulation or altering a proposed one in such a way as to be less distasteful.

Recently, for example, DPW came out with proposed Rule 64, which is designed to prevent or dedect fraud and abuse in welfare payments. It included, for example, a proposal, that welfare employees be allowed to enter physicians' offices, unannounced, to inspect welfare recipient medical records to ascertain the appropriateness of payments claimed. It further would have allowed these inspectors to review private patient's records to ascertain that charges were comparable for similar services.

MMA had earlier made extensive comments on earlier drafts of the proposed rule, but the final draft really did not contain any basic changes. MMA, then in oral and written testimony, presented its objections to the public hearing on the rule, as did other interested parties. The Hearing Examiner agreed with us and did in essence state that the rule should be scrapped and formulation of the rule be started anew. This was exactly what we had suggested.

Whether the Commissioner of Public Welfare and the Attorney General's office comply remains to be seen, but if they do not, they must explain to the public why hearings are no more than window dressing and why the bureaucracy has become a government of and by itself and whether or not it is for the people.

Despite apparent success in influencing government in this and other matters, the victories are somewhat shallow since it remains again a reaction of an action proposed by those to whom society has given such responsibility. While we expend our efforts to better society by attention to the needs of the individual people, government is interested only in the numbers generated by data gathering and compilation, and the final determination is measured in dollars.

We shall continue to achieve and measure other values as well.

Robert S. Flom

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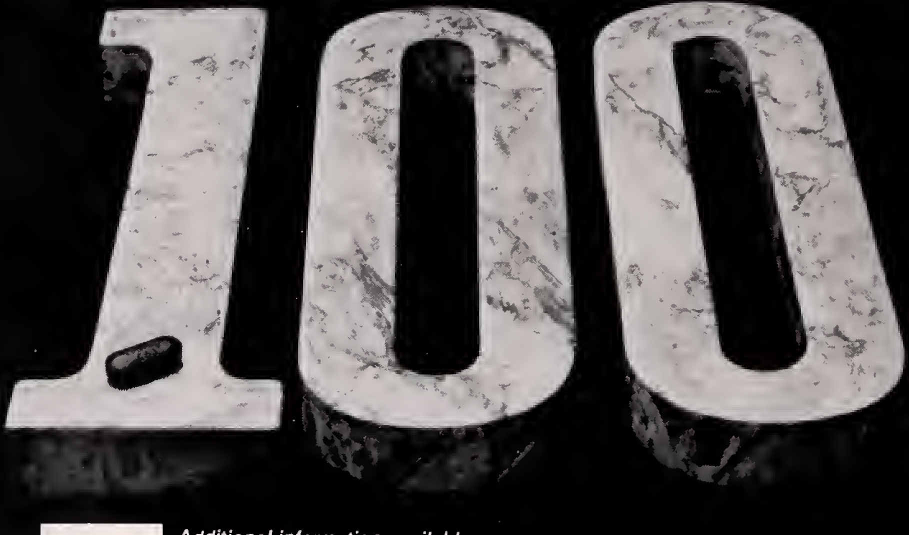

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Editor's Notebook

Postcards from Dubrovnik, London, and Lonsdale

> *"At the root of the nature of travel lie two simple but cogent facts: that contrast always alerts the attention, and comparison enriches the resources, of a healthy mind. As biologists, we have all observed that the simplest kind of locomotion inescapably brings the organism into a new and usually a changed environment. By so much more does travel, the apotheosis of locomotion, assure us of contrast. But travel can bring more than changes. The sensation of contrast provides the basis for a still more intricate and rewarding operation of the mind, namely, comparison and its offspring, analysis, and, in re-synthesis, an amazing sense of freedom."*
>
> *Alan Gregg, M.D., "Travel and Its Meaning",*
> *For Future Doctors, University of Chicago Press, 1957*

Dubrovnik, Yugoslavia
September, 1978

Dear Readers: Contrasts abound in this beautiful country. It is a paradise geographically with rugged mountains, scenic gorges, steep coastlines, and fertile plateaus — and a paradox politically — with its own mix of communism and capitalism. Yugoslavia is a playground for jet-setting Western tourists, yet a showcase for touring Eastern-Bloc communists. It is a Marxist country, which ought to embrace centralized planning, instead it glories in decentralized self-management. It promotes, practices, and juggles "workers' capitalism", "participatory democracy", and "independent communism". And it permits its capitalists to drive Mercedes, build private homes on the Adriatic, and hold foreign bank accounts.

Yugoslavia's six Republics contain these major population groups — Serbs, Croats, Slovenes, Bosnian Moslems, Macedonians, and Montenegrins — and a smattering of Turks, Romanians, Gypsies, Slovaks, Bulgarians, Germans, Czechs, Poles, Austrians, Greeks, and Jews. Small wonder, then, Tito has chosen to hold people together with a decentralized government that caters to local desires.

The health system, we are told, consumes 20 percent of the GNP. The system includes hospital and outpatient services, dental care, glasses, and spas. The commune, the smallest planning unit, contains at least a health station (our equivalent of a small outpatient clinic) and usually has a medical center, a hospital, an Institute of Public Health, a dental clinic, and a pharmacy. Where does money come from to support the system? Mostly from local taxes. How is it dispensed? Mainly through agreements between physicians, hospital employees, local employers, and worker groups. Physicians have a say in what they are paid because they generate their own funds. But fee-for-service does not exist, and individual productivity is not necessarily rewarded. Authorities are mum about physicians' incomes. But you can guess from these Yugoslavian statistics: per capita income $900 (U.S. $6200), population per physician 897 (U.S. 621), and population per hospital bed 170 (U.S. 138).[1]

During our four days here, tour officials arranged for the Medical Adviser of the Dubrovnik Medical Center to speak to us. At first, I felt he was giving us the party line. But when he informed us communes eliminated ''reduplication of health facilities, achieved ''coordinated planning'', and culminated in ''comprehensive integrated health care'', the words reminded me of home. One man's commune, I now know, is another man's Health Service Area. Local officials declined when we asked to see a hospital. But one of our physicians did so on his own. Police arrested and jailed him. The moral: See only what you are shown, or you will see red.

London, England
December, 1978

Dear Readers: I am an anglophile, and this is my fourth London trip. On this visit, I detect restlessness and foreboding about the economic situation. This should be the best of times, the Christmas season, but it is the worst of times, with Christmas spirits sagging, the economy sputtering, and strikes swamping the country. Name any trade union — gravediggers, newspaper reporters, hospital employees, nurses, garbagemen, truckers, or railroad men — and they are striking or threatening to.

I am here to talk before an International Congress of Laboratory Managers. My title ''Crisis in Communication and Productivity''[2] applies more to England as a whole than to its intended audience. Communication between classes — public officials, union people, managers, and ordinary citizens — is bad. Productivity is abysmally low, the worst in Europe. Britain does not produce enough, and its people are demanding more.

Critics blame the aging industrial plant, confiscatory income taxes, and a still formidable class structure. Whatever the causes, a peculiarly British vicious circle has set in: society stagnates, the classes resent the low growth rate, class resentment foments unrest, and unrest prevents growth. Because of entrenched class attitudes and fear of giving incentives or upsetting one's own applecart, hostility and suspicion exist towards innovation, risk-taking, and flexibility — the essential elements of productive societies.

Maybe England is now paying for the Labor Party's policies, initiated after World War II: (1) expansion of the welfare state; (2) heavy estate taxes and redistribution of income; (3) extensive centralized planning; and (4) a sweeping program of nationalization of key industries. These policies make change difficult. Add to these policies the English tendency to look inward for solutions, the hypertrophied moral guilt that sacrifices efficiency and incentives for ''fairness'', and a traditional class structure that represses upward social mobility of the lower and middle classes, and you have deepseated problems.

A word about the National Health Service. As the economy slips and Health Service costs rise, a ''retrenchment drive'' is going on. This drive is cutting back, dropping, or discouraging certain services. Consequently, the queuing lines are lengthening and the logjam of elective surgery cases is piling up. The English people are not happy about this further rationing of services, or the fact that nearly fifty percent of physicians below the consultant level are nonwhite, though they would never do away with ''free'' healthcare. So a Royal Commission is looking into how the Health Service might be streamlined and made more effective.. One Professor of Social Policy and Administration has come up with a novel idea.[3] In a presentation before the Royal Commission, he suggested the Health Service consider turning partly to Private Practice as an effective alternative and as an example of how things might be done. Compared to the entrenched and institutionalized Health Service, he said, Private Practice is flexible, innovative, and quick in responding to public demands. Private Practice, he noted, is here to stay, won't go away, and ought to be part of national policy making. I am sending a copy of his paper to Califano.

To conclude, after 30 years of National Health Service, these defects have become apparent: (1) Health decisions often rest on political expediencies rather than on patient problems. (2) Rationing must ultimately be imposed to cut costs. (3) Government monopoly removes freedom of choice and leads to reduced standards of care or, at best, competent mediocrity. (4) A comprehensive governmental health service may idle, sputter, or choke, but it never dies; for it is politically irreversible.

Lonsdale, U.S.A.
February, 1979

Dear Readers: I know what you are thinking: Where is Lonsdale, and why am I writing a postcard from here? Well, Lonsdale is a village of about 1000, bisected by state highway 19 and nestled into the rolling farm country of southern Minnesota, 45 miles south of Minneapolis and seven miles west of Interstate 35. Seven miles east of 35 is Northfield, a special place that accommodates two colleges.

"You know what highway 35 is?" asks a local sage, "It separates Czechoslovakia from Norway." There is truth to this. Lonsdale citizens are roughly three-fourths of Czech heritage and St. Olaf College in Northfield has strong Norwegian ties. Lonsdale is proud of its heritage, and much of its social and community life revolves around its churches. Lonsdale commands a strong allegiance from its young people. They have formed a thriving Jaycee chapter and are helping older citizens in a drive to preserve the town's two story 1906 schoolhouse. A distinctly Czech cupola surmounts the schoolhouse, which sits on the tallest hill in town.

Why the postcard? My wife and I have been spending a lot of time here, trying to help local citizens restore their schoolhouse. In the course of this restoration project, we have grown fond of the people and have listened to their concerns. One of the principal concerns is this: the only doctor is leaving, and townspeople want another doctor they can call "our own". Community leaders will probably write to the University of Minnesota Medical Placement Center to begin the search for a new physician. But Lonsdale, like similar towns, is not likely to have much luck.

Why not? After all, Lonsdale is a pleasant place, within commuter range of the Twin Cities, and according to the billboard at the edge of town, is a "growing community". And, as a state, Minnesota's three medical schools have purposefully recruited small town students (with the hopes they would return home); have conducted a successful rural preceptor program; and have developed more family practice resident positions per capita than any other state. Besides, for the first time in fifty years, more Americans are migrating back to rural areas than are coming to the cities. Anyway, as Lonsdale citizens are fond of telling me, the physician's income would be "no problem" and any physician would be "busier than he wants to be."

Which brings me to my reasons for composing this card: to analyze contrasts between expectations of rural citizens about physicians practicing alone in rural areas and the realities. The odds of any young physician going into solo rural practice are infinitely small.

Most young doctors prefer group practice because (1) they wish to practice with adequate consultation; (2) they desire reasonable working hours, coverage while away, and time with their families; (3) they have not been extensively trained in surgery or complicated obstetrics and do not want to handle massive trauma cases alone; (4) they fear medical legal consequences from inexperience, excessive busyness, or hasty decisions; (5) they have come to rely on technology, particularly on radiologic and laboratory support; (6) they dread professional isolation from peers after spending so many years in academic or hospital settings; (7) they know most groups are in regions with sufficient population to provide the amenities and services to which educated young physicians and their families have become accustomed. What do these factors have in common? All have to do with knowledge. Young physicians are knowledge people, and they know knowledge — whether it comes from technology or from other knowledge workers within a health care organization — is what makes them effective.

A contrast often exists between what small towns "want" and "need". Lonsdale ''wants'' its own physician, but does it ''need'' one? After all, Lonsdale is only 65 miles from the Mayo Clinic and 45 miles from the Twin Cities, and Lonsdale people regularly go to specialists in both places. Besides, 12 to 20 miles in any direction, without obstructing stop signs or traffic lights, you can reach at least 33 physicians, and three hospitals. Northfield, 15 miles to the east, has 11 physicians and a 86 bed hospital. Faribault, 20 miles to the southeast, has 13 physicians and a 103 bed hospital. New Prague, 12 miles northwest, has eight physicians and another 60 bed hospital. And Montgomery, 12 miles to the southwest, has a family practitioner. For emergencies, Lonsdale has a contract to use a Northfield ambulance, and Lonsdale is raising funds for a Rescue Squad vehicle.

Still, Lonsdale would like a physician. But the hard reality is that health services are not evenly distributed between urban and rural areas — in the United States, in Russia, in Scandinavia, or anywhere in the world. Nor are any other services, with the possible exception of postal and telephone services. Everywhere lawyers, accountants, architects, engineers, and other professionals congregate in metropolitan regions. As long as people are free to choose where they live, services will be unequal.

This explanation will not make Lonsdale citizens feel any better. Like all of us, they would like personal and constant access to their own physician. But there is hope: Minnesota is training more family practitioners, and graduates are migrating back to rural regions in organizational settings where they can effectively apply their knowledge. Who knows? Maybe a group of enterprising young physicians will decide to form a clinic here. Lonsdale will be ready.

Richard L Reece MD

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Asthma
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Profundoplasty
Varicella Zoster

CME at the
MMA Annual Meeting, May 17, 18, 1979

Traumatic Atlantocranial Dislocation with Survival

GAYLAN L. ROCKSWOLD, M.D.* and EDWARD L. SELJESKOG, M.D.*

The authors present a multiply injured patient with craniocervical dislocation who survived. Various aspects of the management of this problem are discussed.

TO OUR KNOWLEDGE there are only five previously reported cases of traumatic atlantocranial dislocation with survival.[1,2,3,4,6] The purpose of this article is to describe such a case and discuss various aspects of the management of this problem.

Case Report

This seven-year-old boy was admitted to the Hennepin County Medical Center on September 26, 1976 following an automobile-pedestrian accident. Cardiopulmonary assistance had been administered at the scene of the accident by a physician. Upon arrival at the Hennepin County Medical Center emergency room the patient was unresponsive to verbal stimuli. There was movement of the extremities to painful stimuli but a right hemiparesis was evident. In addition, there were bilateral VI cranial nerve palsies.

A nasotracheal tube was inserted using a "blind" technique without movement of the neck. Standard cervical x-ray examination with the head immobilized revealed a probable craniocervical dislocation (Figure 1). A fracture of the right femur was also noted. The patient became hypotensive. A peritoneal tap revealed gross blood. The neck was immobilized in a hard cervical collar, sandbags were placed along the head and neck, and the patient was taken directly to the operating room. A ruptured spleen, a severely lacerated left kidney and large retroperitoneal hematoma were identified, necessitating a splenectomy and a left nephrectomy. Postoperatively, with the patient still under general anesthesia, computerized axial tomography was obtained which revealed evidence of brain stem contusion and edema. The patient was subsequently placed on a circle bed and skeletal traction was applied using four lbs of weight. The weight was subsequently reduced to 1 lb and lateral head support was continued with sandbags.

The patient remained unresponsive to verbal stimuli for approximately one week and then began to show progressive improvement. A tracheostomy was performed on October 4, 1976.

Subsequent neurologic examination revealed the patient to be alert and lucid with bilateral VI nerve palsies, decreased IX and X cranial nerve function bilaterally, a right XII nerve dysfunction and a tetraparesis, worse on the right. There was bilateral ankle clonus and Babinski toe signs were present. Speech was severely dysarthric and of low volume. On October 25 the patient was placed in a body cast with a Halo attachment to improve cervical stability and allow some degree of patient mobilization.

The patient was transferred to the Physical Medicine and Rehabilitation Unit at the University of Minnesota Hospitals on November 22. Subsequently, he developed a skin infection under the

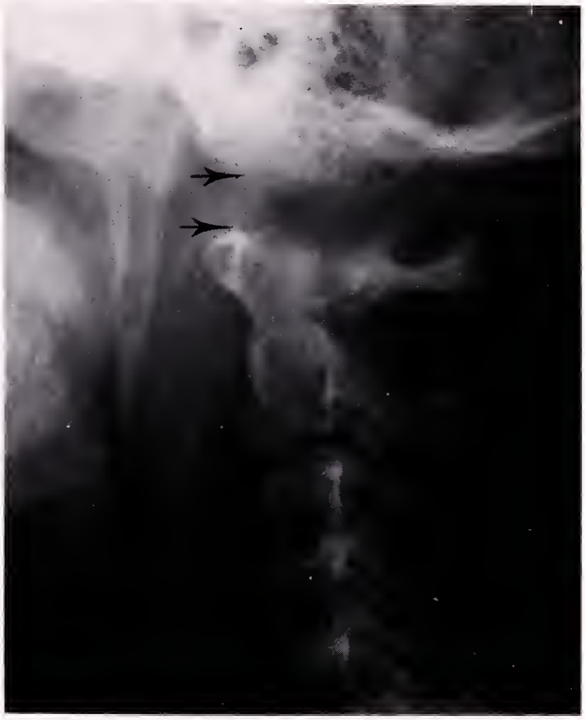

Fig. 1—Initial lateral roentgenogram of the cervical spine taken in the emergency room revealing the atlantooccipital dislocation.

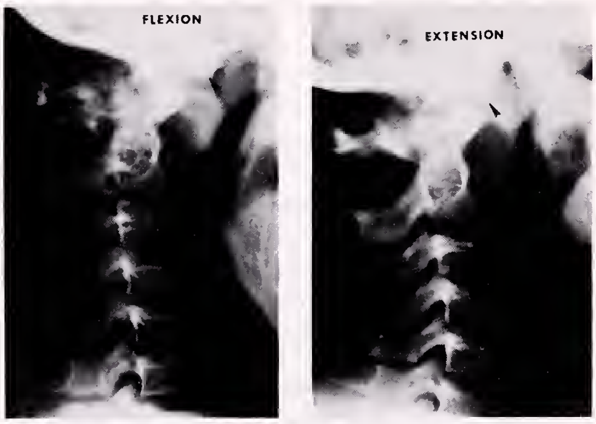

Fig. 2—Flexion-extension views of the cervical spine reveal gross instability at the occipitoatlantal junction.

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*Division of Neurosurgery, Hennepin County Medical Center, and Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota.

Send requests for reprints to: Gaylan L. Rockswold, M.D., Division of Neurosurgery, Hennepin County Medical Center, Minneapolis, Minnesota 55415.

body cast and it was removed. Carefully obtained dynamic films revealed the cranial-cervical dislocation to be grossly unstable (Figure 2).

An atlantooccipital fusion was performed on January 3, 1977. The patient was turned prone on the circle bed and positioned while awake. A lateral cervical spine film was taken to document the position of the cervical spine. Only then was the patient anesthetized via his tracheostomy. The fusion consisted of passing a #20 gauge wire around the arch of C-1 and then between two paramedian burr holes placed near the foramen magnum of the occipital bone. The atlantooccipital area was then packed with cancellous bone chips after roughening the exposed bony surfaces (Figure 3). Subsequently the patient was again placed in a Halo cast.

The patient remained in the Halo for approximately 3 months and now appears to have a solid fusion (Figure 4). He is able to ambulate with support and a good functional recovery is anticipated.

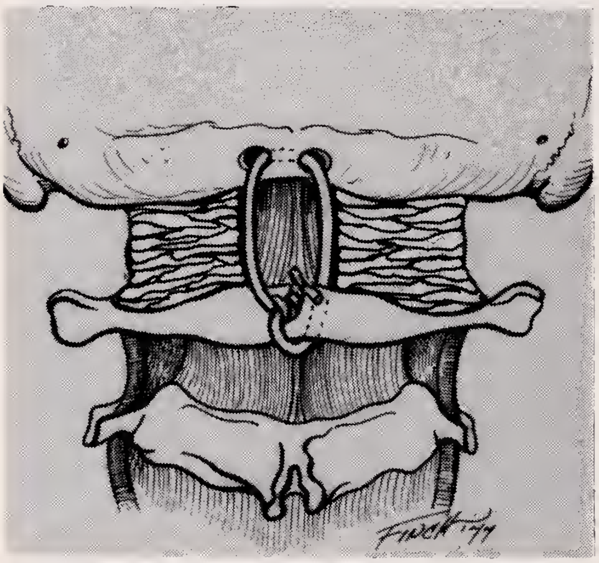

Fig. 3—Diagramatic sketch of operative fusion performed in this patient. Note the wires around the arch of the atlas and through 2 burr holes at the edge of the foramen magnum.

Discussion

The occipito-atlanto-axial joints are a complex unit which provide for universal motion of the head with respect to the spine.[5,7] Lateral rotation occurs primarily at the atlanto-axial articulations with some mild degree of flexion-extension movement also occurring at this joint. Most flexion-extension of the head occurs at the atlanto-occipital joints.

According to Werne, the ligamentous connections of the craniocervical junction are stronger than the bony joints and must be severed in order for dislocation to occur.[7] Although the evidence is not conclusive, a severe hyperextension of the head on the spine is probably the mechanism for this dislocation.[1,4,6] There was no definite history nor were there signs of the specific type of injury that occurred in this case.

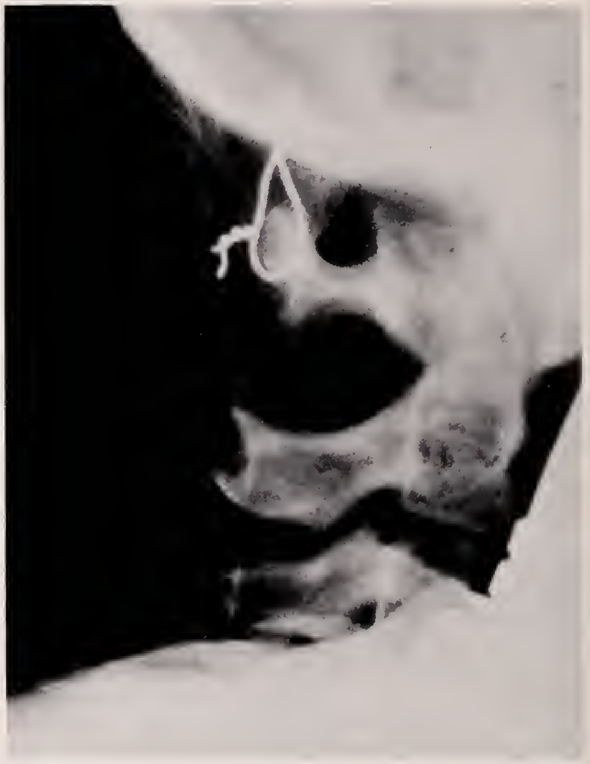

Fig. 4—Lateral cervical spine view obtained 3 months after occipital-atlas fusion.

The initial management of a patient with an unstable atlantooccipital joint is obviously critical. An airway is mandatory and yet no motion can occur during intubation or tracheostomy. "Blind" nasotracheal intubation or immediate tracheostomy are recommended for respiratory distress.

Excessive amounts of weight applied to traction on the neck should be avoided or unexpected dislocation can occur.[4,6] In the pediatric age group good immobilization with bed rest and traction is difficult. We elected to place the child in a Halo cast relatively early to allow complete immobilization of the dislocation as well as early patient mobilization.

Experience with this injury is so limited it is impossible to make a definitive statement regarding the advisability of operative fusion. In four of the five previous case reports, however, operative fusion was required for permanent stabilization of the dislocation.[2,3,4,6] In one report a very satisfactory result was achieved with external immobilization for one year. It would seem to us that the significant ligamentous type of injury in this dislocation would make it subject to chronic instability when there is treatment only by external immobilization. It would appear that most cases will require some form of internal fixation and fusion.

References will be found on page 154

Enucleating Donor Eyes and Uses of Donor Eyes

RONALD LINDE, M.D.*

In Minnesota and elsewhere ophthalmologists, doing transplantations, have a constant need for donor tissue.

RELATING TO THE next of kin and the technique of enucleation are barriers to the acquisition of donor tissue.

Some of the best donor tissue comes in the event of unexpected death, and requesting this donor tissue is often awkward. Sometimes simple explanations are helpful, but each physician knows how he best handles the situation. This will vary, of course, depending upon the donor and the next of kin. An informed public is also helpful. Office distributions are available to acquaint patients with the Minnesota Lions Eye Bank.

The interval between death and enucleation should be as short as possible. Clear corneal grafts have been obtained with intervals up to twelve or more hours. Cooling the body (if possible) and/or ice packs over the closed eyelids are helpful in cases where enucleation is delayed beyond six hours.

Corneal retrieval may be performed by an M.D. or any other person deemed qualified by the Medical Director(s) of any eye-bank of the Eye-Bank Association of America, Inc. In Minnesota morticians and ophthalmic technicians can also perform enucleations if they are trained.

The enucleation should be performed by sterile technique. After preparation of the site, the eyes are removed using the following technique. A circumcorneal incision is made about 3mm from the limbus (corneal-scleral junction). The conjunctiva and Tenon's capsule are dissected from the sclera beyond the rectus insertions. A muscle hook is introduced beneath each rectus muscle, sparing the lateral rectus muscle. Traction is exerted on the muscle hook as each rectus muscle is divided. The globe is rotated inward using the muscle hook beneath the lateral rectus muscle. Enucleation scissors are made to straddle the optic nerve, which is severed away from the globe to obtain a long nerve stump. The lateral rectus muscle and any remaining connective tissue strands are divided close to the eyeball. The person removing the eyes should take great care not to inadvertently open the globe.

Following an enucleation the globe is irrigated with a sterile solution. The globe is carefully placed in a sterile glass container in such a manner that the cornea does not touch the wall of the container. To position the globe properly, sterile gauze or cotton may

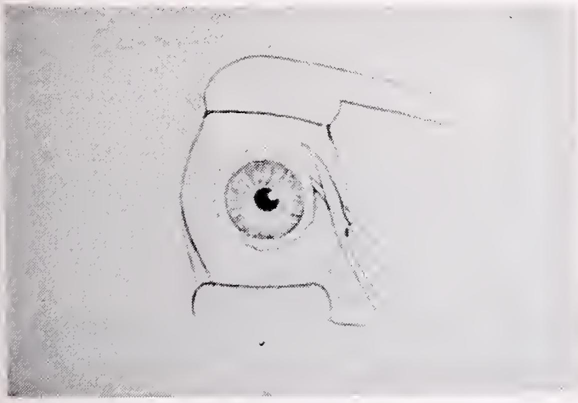

Fig. 1 — Dissecting conjunctiva and Tenon's capsule.

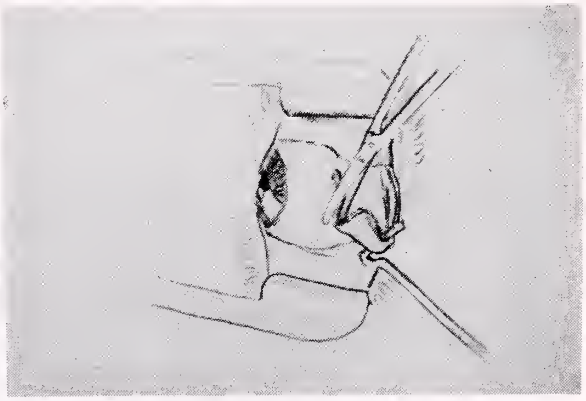

Fig. 2 — Dividing rectus muscle.

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*Northfield, Minnesota.

Presented at the Southern Minnesota Medical Association Meeting in Owatonna, Minnesota, September 23, 1978.

be used in the glass container. The gauze may be moistened with sterile normal saline or sterile water as the globe should be in a moist atmosphere. The glass container is then placed into the shipping container, keeping the contents as cold as possible without freezing. The State patrol will transport the donor tissue to the eye station at the University of Minnesota Hospitals.*

Clear corneal grafts are more likely from fresh transplants. Donor tissue can also be preserved by the McCarey-Kaufmann technique or cryopreservation for possible corneal or scleral transplantation. When there are known donor conditions that preclude surgical transplantation (i.e., generalized sepsis, leukemia, disseminated viral infections, retinoblastoma, or neurological conditions caused by a virus), the eyes can be used for research and teaching purposes.

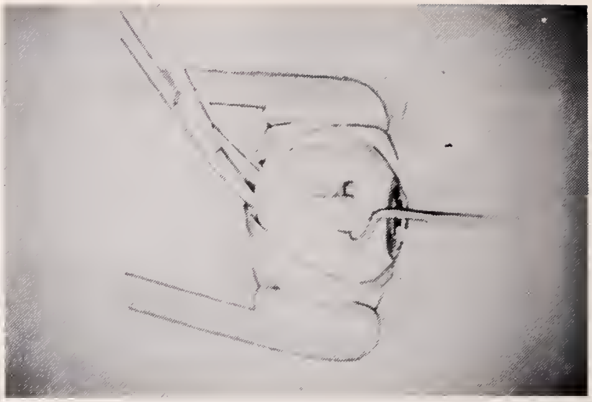

Fig. 3 — Severing optic nerve.

The decision to request donor tissue often rests with the physician. This physician responsibility is eased by an informed public and a confident physician, acquainted with the enucleation procedure.

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*The University of Minnesota Hospital Eye Bank will provide further information as to the procurement of the glass containers as well as the shipping containers that the Minnesota Lions Clubs have donated.

University of Minnesota Eye Bank
University of Minnesota Hospitals
Ophthalmology Department
Minneapolis, Minnesota

Traumatic Atlantocranial Dislocation with Survival – Rockswold and Seljeskog (page 152).

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Harold W. Brunn JD

Harold Brunn, Executive Vice President of the Minnesota Medical Association, has been elected again to the Board of Directors of the Professional Convention Management Association which represents medical, dental, hospital and allied professions.

Skiing Injuries to the Urinary Tract

T. A. HILDRETH, M.D.,* A.S. CASS, M.D.* and A. U. KHAN, M.D.*

Ski related urologic injury mainly involves the kidney and is associated with other abdominal organ injury rather than orthopedic injury. Most injuries occurred late in the day when reduced visibility and fatigue could have been contributing factors.

ESTIMATES OF THE injury rate from skiing range from 3 to 10 per 1,000 skiers per day.[1,2] Annually this amounts to between 150,000 and 225,000 skiing injuries. Though the majority of these (more than 80%) injuries are orthopedic in nature,[3] urologic injuries are being increasingly recognized. Ski related urologic injuries have not often been reported; we have thus reviewed our experience over the last eight years and present it herein.

Clinical Material

Between 1969 and 1977, eleven patients were injured while downhill skiing. Urologic injuries were suspected when trauma involved the flank, abdomen or pelvis and in the presence of gross or microscopic hematuria. Infusion excretory urography was performed and was followed by renal arteriography when the IVP showed non-function or renal parenchymal damage. Cystograms were obtained in the majority of patients and also retrograde urethrograms, where indicated.

Results

Of the eleven patients who sustained ski-related urologic injuries, six patients had significant intra-abdominal injury (laceration of the spleen in four, of the liver in one, and mesenteric hematoma in one), requiring laparotomy (Table). In those patients in whom a description of a specific nature of trauma was recorded the most common cause of injury was loss of control and balance resulting in a fall on the ground. Most ski injuries (nine out of eleven) occurred late in the day. Two patients described injuries resulting from the ski pole being thrust into the flank while trying to maintain balance. Both of these patients underwent nephrectomy; one because of a previously diseased, hydronephrotic kidney and the other because of an extensive renal rupture without other significant abdominal trauma.

Discussion

With increasing popularity of winter sports, especially downhill skiing, sports-related injuries are becoming more common. While orthopedic injuries involving the long bone of the lower and upper extremities are by far the most common type of injury,[1] blunt abdominal trauma due to collision with trees or tree stumps, ski poles, or just from a fall on the ground may result in a significant injury to the kidney. In six out of ten patients who sustained renal injury while skiing, there was significant associated intra-abdominal injury requiring laparotomy. Only four of these ten renal injuries underwent immediate surgical management; repair of laceration in one and nephrectomy for rupture (shattered) kidney in three patients. In none of these patients was there any external evidence of flank trauma.

TABLE
Ski Related Urologic Injury and Its Management

Site of Injury		Nature of Injury	Associated Injuries		Treatment of Urologic Injury
Urethra	1	Contusion — 1			Conservative
Kidney	10	Contusion — 6	Ruptured Spleen	3	Conservative (1-Subsequent nephrectomy for large pre-existing hydronephrotic kidney)
			Mesenteric Hematoma	1	
			Femur Fracture	1	
		Laceration — 1	Liver Laceration	1	Repaired
		Rupture — 3	Ruptured Spleen	1	Nephrectomy

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*Department of Urology, St. Paul-Ramsey Hospital, St. Paul, Minnesota.

Requests for Reprints to: A. S. Cass, M.B.B.S., Chief, Department of Urology, St. Paul-Ramsey Hospital, 640 Jackson Street, St. Paul, Minnesota 55101.

See editorial page 175.

Unlike ski-related orthopedic injuries that have a definite pattern related to the stress shears and change in forces on the long bones, there was no definite pattern of renal injury that could be considered characteristic of ski-related trauma. When signs and symptoms are out of proportion to the severity of the injury, pre-existing renal pathology must be suspected and a complete investigation is in order, as in one patient with a large hydronephrotic kidney. There was only one case of injury to the external genitalia by the ski and this injury was a urethral contusion. It is interesting to note that the majority of the ski injuries occurred late in the day which is consistent with the contention that fatigue and poor lighting may contribute to ski accidents. Most of the ski injuries seen at our hospital came from one particular ski area. This probably is an indication of the proximity of the hospital to this particular ski slope and the popularity of the ski slope rather than a reflection of the skiing conditions in this ski area.

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MMA ANNUAL MEETING MAY 17-18, ST. PAUL

You've been invited to St. Paul on May 16-17-18 for the 1979 MMA Annual Meeting. Ramsey County Medical Society and Auxiliary are anxious to show you the best of the capitol city.

Maybe you've decided to come on Friday for a specialty society meeting or a CME course. You might be there Thursday too — another full day of CME, the luncheon, the banquet. Delegates attend the opening session of the House on Wednesday. You'll be welcome whenever you arrive, but I'd like to tell you more about what's going on Wednesday, May 16.

If you're a tennis player or golfer, you might have made the annual tournaments a tradition already. For runners, foot races have been added to the schedule this year. Athletic events all begin Wednesday morning.

General registration is open Wednesday afternoon and evening. This could save you time and confusion by picking up your materials early, not when you're trying to get to class on time. Think about it, you can walk in and be seated on Thursday morning without standing in line if you visit the registration desk Wednesday.

If it's entertainment you're after, try The New Wizard Oil Troupe, ''A Medicine Show,'' 6:00 pm on Kellogg Boulevard in front of the Radisson Hotel. The Minnesota of a century ago comes alive in their authentic re-creation of an 1880's medicine show. Afterward socialize with your colleagues and visit the exhibits at the Annual Meeting Reception. Complimentary hors d'oeuvres and cash bar in the exhibit hall conclude the scheduled activities for the day. There's still time for dinner at one of St. Paul's fine restaurants.

Come for an afternoon or come for the entire meeting. We hope to make your visit worthwhile whatever you decide. Just remember Wednesday, May 16 when you receive your advance registration materials by mail and you're marking your calendar. Remember golf, tennis, running, the medicine show, the reception and exhibits, the St. Paul restaurants. Remember the people who will come at the last minute Thursday morning and stand in line to register.

Remember Wednesday, May 16 in St. Paul — we hope to see you then!

S. V. Thorson M.D.
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Cadaver Kidney Transplantation
Effect of Hypotension and Donor Pretreatment with Methylprednisolone and Phenoxybenzamine

by

LUIS H. TOLEDO-PEREYRA, M.D., PH.D.;* RICHARD L. SIMMONS, M.D.;* LESLIE C. OLSON, B.A.;*
JOHN S. NAJARIAN, M.D.*

Hypotension in cadaver kidney donors was associated with a higher incidence of acute tubular necrosis only if it was present both before and during nephrectomy. As soon as the kidneys recovered from acute tubular necrosis they functioned as well as the unaffected kidney.

Cadaver donor pretreatment with methylprednisolone or phenoxybenzamine did not significantly modify the short or long-term function of perfused cadaver kidneys.

THE CIRCULATORY status of a cadaver kidney donor may have direct effect on preservation and transplantation results of the donated organs. Cadaver kidneys that undergo more than 60 min of severe hypotension or warm ischemia frequently develop acute tubular necrosis (ATN) immediately after transplantation. Many attempts have been made to ameliorate the donor's hypotension and prevent pretransplant ischemic damage in order to improve the function of the transplanted kidneys. We report the effect of the donor's circulatory condition, as well as the effect of methylprednisolone and phenoxybenzamine, on the short and long-term function of kidneys transplanted from cadaver donors.

Material and Methods

Between June 22, 1971 to August 23, 1973, 92 consecutive human cadaver kidneys were preserved by hypothermic pulsatile perfusion with cryoprecipitated plasma for varying lengths of time (average 18 hr) prior to transplantation. The standard techniques for operation and immunosuppression have been described.[1] All recipients have been followed a minimum of 24 months. The actuarial survival of all kidneys was calculated by the method of Merrell and Shulman.[2] All causes of kidney loss including death are represented in the Figures. Renal function was defined as that sufficient to sustain life and not require dialysis. Acute tubular necrosis (ATN) is a clinical diagnosis mainly based on the patient's need for at least a single episode of hemodialysis. Permanent reinstitution of dialysis, graft removal or patient death were all considered signs of graft failure.

The effect of the cadaver donor hypotension on the recipient renal function was assessed in 82 of the 92 patients who received kidneys. Thirty-five of 82 donors were hypotensive at one time or another. Forty-seven of 82 donors were the controls with neither hypotension nor pretreatment during harvesting. Hypotension is defined as the donor systolic blood pressure below 90 mmHg and the diastolic pressure below 60 mmHg before or during the donor operation (or both) for a minimal period of one hour.

The effect of donor pretreatment with methylprednisolone and phenoxybenzamine on the function of kidneys obtained from cadaver donors was studied in 33 patients. Phenoxybenzamine (0.75 to 1.5 mg/kg) was administered to 10 donors 60 minutes before nephrectomy. Methylprednisolone (20 to 40 mg/kg) was given to 23 donors 60 to 90 minutes before the kidneys were removed. Fifty-nine of 92 donors were the controls who received no pretreatment at all. All donors had adequate hydration and received furosemide (0.5 to 6.0 mg/kg) or mannitol (12.5 gm), or both, before or during nephrectomy.

After nephrectomy each kidney was washed out with (4°C) lactated Ringer's solution containing 10,000 U/L of heparin sodium and 0.1 gm/L of procaine hydrochloride. The kidneys were preserved in the Mox-100 hypothermic pulsatile perfusion system with cryoprecipitated plasma.[3]

Histocompatibility testing was performed on peripheral blood donor lymphocytes and lymph node cells removed at the time of donor nephrectomy.

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Recipient cytotoxic antibodies directed against donor cells were studied by the microlymphocytotoxicity method of Amos and associates.[4] No patient with cytotoxic antibodies to the donor tissue received a kidney.

Results

Forty percent of the 35 kidneys that had hypotension at any time before transplantation developed ATN whereas only 25% of the 47 kidneys with no period of hypotension developed ATN. If the period of hypotension was limited only to the time of the donor nephrectomy, 20% of the kidneys had ATN; when the hypotensive period occurred before nephrectomy, 33% of the kidneys underwent ATN. Neither hypotension, at any time, nor ATN had any detrimental effect on the long-term (24 months) function of the grafts that recovered function (Figure 1).

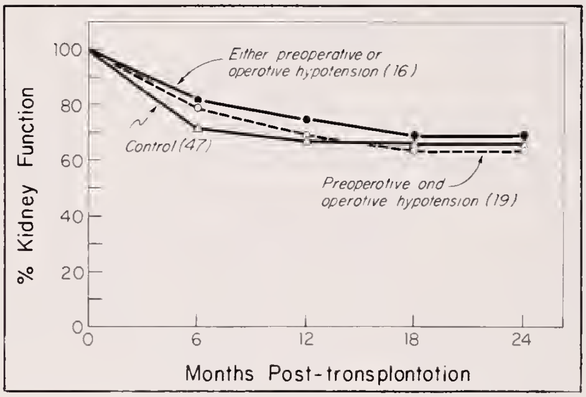

Fig. 1 — Actuarial survival of functioning kidney grafts. Long-term (24 months) kidney function of control kidneys (without hypotension), and kidneys with hypotension either before or during nephrectomy, or both.

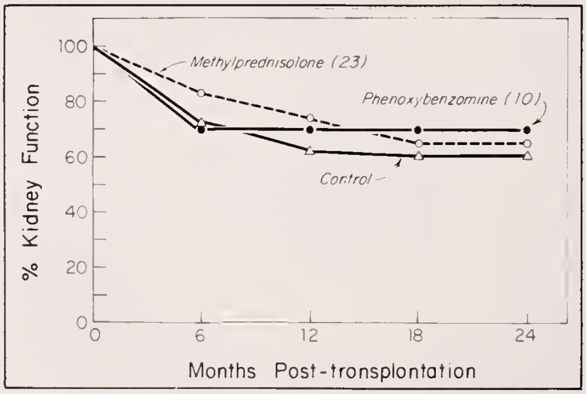

Fig. 2 — Actuarial survival of functioning kidney grafts. Long-term (24 months) function of kidneys from untreated (control) cadaver donors, or donors treated with either phenoxybenzamine or methylprednisolone.

There was no difference in the incidence of ATN among the control kidneys (35%) (twenty of fifty-nine patients) and those treated with methylprednisolone (30%) (six of twenty-three patients) or phenoxybenzamine (40%) (four of ten patients) before donor nephrectomy. In addition the dose of methylprednisolone made no significant difference. Twenty-nine to 33% of the kidneys developed ATN when the donor was pretreated with more than 30 or less than 30 mg/kg of methylprednisolone respectively. Likewise, there were no significant differences in long-term graft function between any of those three groups (Figure 2). The preservation time was similar in the control and treated or hypotensive groups.

Discussion

Hypotension in cadaver kidney donors had a deleterious effect on the immediate function of grafted kidneys only if it was present both before and during nephrectomy. Hypotension did not cause any long-term detrimental effect; as soon as the kidneys recovered from ATN they functioned as well as the unaffected kidneys. This data confirms our previous experience that the early immediate posttransplant function is not of ultimate prognostic importance.[5]

Cadaver donor pretreatment prior to nephrectomy has been used regularly in most transplantation centers to minimize the ischemic damage to the harvested organ.[6] Ischemic damage and hypotension each produce vascular spasm, endothelial edema and platelet aggregation. The aerobic metabolism decreases, the cellular sodium pumps begin to fail and the pH falls. If the ischemia is severe, the lysosomal membranes may also rupture. Methylprednisolone, phenoxybenzamine, mannitol and furosemide have been used to protect the kidney from these ischemic or hypotensive cellular changes.

Miller and Alexander,[7] used methylprednisolone to protect ischemic canine kidneys. The most beneficial effect was seen in the organs that received the drug 120 minutes prior to the ischemic insult. We have also demonstrated a beneficial effect of methylprednisolone in dog kidneys treated before the ischemic injury had been applied.[8] McCabe[9] showed a reduction in the incidence of ATN when human cadaver donors were treated with methylprednisolone (30 mg/kg) one to two hours before nephrectomy.

It is difficult to determine the real effect of methylprednisolone in the hypotensive donor by the retrospective data obtained from this study. The nephrectomies took place in the donor's hospital under ideal conditions, the ischemic insult was minimal, and a significant number of patients were not hypotensive.

Phenoxybenzamine, an alpha adrenergic blocker, has been used extensively in treatment of kidney donors. Belzer and Kountz[10] improved the short-term kidney function of cadaver kidneys from donors treated with 1.0 to 1.3 mg/kg of phenoxybenzamine 30 minutes prior to nephrectomy. Rangel and his co-workers[11] and Bell and his group[12] have also demonstrated the beneficial effect of this drug on ischemic kidneys.

The small number of kidneys treated with phenoxybenzamine does not permit us to draw definite conclusions. Furthermore, the dose ranged from 0.75 to 1.5 mg/kg given 60 minutes before kidney excision. These kidneys also probably had *minimal hypotensive damage with no vasospasm involved.*

In summary, hypotension in the cadaver donor is associated with a higher early incidence of ATN in the grafted kidney. This effect is more evident when hypotension is present both before and during donor nephrectomy. If the donor's hypotensive state is present at a single time, either preoperative or operative, there is a less significant deleterious effect on the transplanted kidney. At any event, when the kidney recovers after dialysis, there is no detrimental effect on the long-term kidney function.

Under the conditions of this retrospective study, phenoxybenzamine given intravenously at doses of 0.75 to 1.5 mg/kg, 60 minutes before donor nephrectomy, or methylprednisolone at doses of 20 to 40 mg/kg given 60 to 90 minutes prior to kidney removal, does not modify the short or long-term function of perfused cadaver donor kidneys.

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Cover Photograph

"Early Spring in Minnesota"

The picture was taken in Northeastern Minnesota, close to the Red River Valley in early May. Dr. Carl Kjellstrand and his wife were driving back to a campground after one day of bird watching. It was a beautiful mild evening with all the romance of early spring. The sun was setting quite red through clouds in a dramatic fashion with the dead trees in the foreground. The trees were elms. Death seemed all around, but with all the hopes of early spring around it.

The picture was taken freehand on Kodachrome 64ASA film with a Vivitar Series 1 telephoto zoom 70-120 mm, set at 210 mm. The F setting was 5.6, and the actual time about 250ths of a second. The sun is centered where the light meter reads most; so Dr. Kjellstrand achieved a deliberate under-exposure of the countryside below the sky.

Dr. Carl Kjellstrand is a Professor of Medicine and Surgery and Chief of the Nephrology Section at the University of Minnesota. He graduated from the University of Lund in Sweden in 1962, but since then has lived in the United States except for the years 1965, 1966 and 1967 when he continued training in Sweden. His family and he became American citizens in 1978.

Laboratory Letter

The Laboratory Evaluation of Thyroid Function

MICHAEL W. STEFFES M.D., Ph.D.* and JACK H. OPPENHEIMER M.D.*

THE PRACTICING PHYSICIAN faces an enlarging array of endocrine procedures offered by laboratories at his own hospital or through reference services. This explosion in available radioimmunoassay methodologies has become especially prominent in thyroid function testing; however, the change comes at a time when research in thyroid hormones and their actions has demonstrated instances in the clinical setting where thyroid function testing may be inconclusive and in some cases misleading.[1] This discussion presents some current methods of thyroid function testing and suggests a fundamental array of tests, some of their limitations and basic recommendations for their use.

Thyroid Hormones

Methodologies utilizing radioimmunoassays have generally replaced older tests such as the measurement of protein-bound iodine (PBI) and the estimation of thyroxine (T_4) by the competitive protein-binding method of Murphy-Pattee.

Thyroxine or Tetraiodothyronine (T_4)

The measurement of T_4 will, in most patients, reflect the state of thyroid function. In terms of production by the thyroid gland and levels in serum, T_4 is the predominant thyroid hormone. On a weight basis it is not as biologically potent as triiodothyronine (T_3). The major amount of T_3 present in serum is derived from extra-thyroidal conversion of T_4 to T_3, and it is uncertain what portion of the biological action of T_4 is mediated through its conversion to T_3. Most laboratories currently measure T_4 by radioimmunoassay (RIA). There are many commercial sources for this assay, and most procedures provide comparable results. Each laboratory should establish its own normal range and be apprised of instances where this procedure may give misleading answers (see section on Problems of Thyroid Function Testing).

Triiodothyronine (T_3)

T_3 is more potent than T_4 and present in smaller amounts in serum. In general, the measurement of T_3 should be used only in cases of suspected hyperthyroidism. In many commonly encountered clinical situations a T_3 level may be misleading. In patients with non-thyroidal illness the value may be spuriously low, and in patients with suspected hypothyroidism, it may be low or normal.

T_3 is measured by radioimmunoassay, but unlike the T_4 RIA substantial methodologic differences are observed with the T_3 RIA. Thus each laboratory must select a methodology and obtain its own normal range.

Thyroid-Binding Proteins

Although one can measure thyroid binding globulin by RIA, the two most frequently utilized methods accounting for levels of T_4 and the thyroid-binding proteins are the Thyroid Index (adjusted T_4 or Free-T_4 index) and the Free-T_4.

Thyroid Index and T_3-uptake

The T_3-uptake reflects the protein-binding of labeled-T_3 added to a serum sample. By one technique (Method 1) it is reported as the percent of ^{125}I-T_3 absorbed by inert particles (silica, resin, or charcoal) added to the serum — in other words, the percent of labeled T_3 not bound by the patient's thyroid binding proteins (Percent $\frac{\text{Counts on silica}}{\text{Total Counts}}$). As an alternative to expressing the results as percent of label absorbed by the inert particles, the T_3-uptake may be reported as the ratio of the ^{125}I-T_3 uptake in the patient's serum to the average uptake of normal pooled serum; i.e., $\frac{\text{Counts on silica — patient}}{\text{Counts on silica — normal}}$. A normal value is unity.

The T_3-uptake expressed as a ratio can be used with the T_4RIA to derive the Thyroid Index, the product of the two, and a value accounting for levels of T_4 and the thyroid-binding proteins:

$$\text{Thyroid Index} = T_4 \times T_3\text{-uptake}$$

An alternative procedure (Method 2) of calculating the T_3-uptake divides the counts accepted by the inert material by the counts remaining in the serum $\left(\frac{\text{Counts silica}}{\text{Counts serum}}\right)$. This number can be used with a value similarly derived from normal pooled serum to calculate a ratio of patient to normal; i.e., $\frac{\text{uptake patient}}{\text{uptake normal}}$. Again a normal value is unity. The thyroid index may be determined as above using the T_4 and T_3-uptake values.

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In most patients the Thyroid Index calculated by either method will provide adequate information regarding thyroid function, accounting for both T_4 and TBG levels (Table). In pregnant women and women taking estrogens, patients demonstrating elevated TBG and T_4 levels and corresponding low T_3-uptake values, the Thyroid Index calculated using Method 2 yields values in the women studied closer to those of a normal population than does Method 1 (Table).

Free-T_4-

The Free- T_4 estimates the free fraction of T_4 not bound to thyroid binding proteins; i.e., the putative active portion of the hormone. In the procedure labeled-T_4 added to patient's serum equilibrates with the free and bound hormone. The free fraction is estimated by determining the dialysable portion of the added label. The free fraction is then multiplied by the total T_4 (as determined by conventional methods) to yield the Free-T_4 level:

$$\text{Free-}T_4 = T_4 \times \text{dialysable fraction}$$

In most instances encountered clinically the Free-T_4 correlates well with the Thyroid Index.[2] Ranges for Free-T_4 must be established in normal people, in patients with hypo- and hyperthyroidism and in people with non-thyroidal illness.

Thyroid Stimulating Hormone (TSH)

This hypophyseal peptide stimulates production of thyroid hormones by the thyroid gland. In turn TSH secretion is regulated by the levels of thyroid hormones in the blood through a feedback mechanism at the pituitary and by the secretion of thyrotropin releasing hormone (TRH) by the hypothalamus. In a hypothyroid patient, a high TSH value is consistent with a primary defect in thyroid function; i.e., the lack of production of thyroid hormone by the thyroid gland results in failure of negative feedback at the pituitary gland. Therefore, high serum TSH values will be observed following increased hypophyseal secretion of TSH. In hyperthyroid patients, serum TSH levels should be suppressed to subnormal values; however, in practice they may be indistinguishable from those of normal people, thus reducing the utility of the test in hyperthyroidism. TSH is measured by radioimmunoassay. With a variety of methods available, each laboratory must establish its own normal range. Its principal use pertains to evaluation of suspected hypothyroidism.

Thyrotropin Releasing Hormone (TRH) Test

The TRH test employs synthetic TRH (a tri-peptide) to stimulate release of TSH from the pituitary gland (measured by the increase in TSH levels in sequential serum samples obtained following administration of TRH). Despite encouraging initial results in distinguishing hypothalamic and hypophyseal hypothyroidism, the test lacks sensitivity and specificity. Appropriate and helpful employment of the TRH test lies in the elucidation of borderline hyperthyroidism when the T_4 and T_3 levels are equivocal. A failure to respond to TRH is compatible with hyperthyroidism.

Problems with Thyroid Function Tests In Patients with Non-Thyroidal Disease

Often a patient with serious illness presents with clinical features compatible with hypothyroidism, and to complicate the evaluation, alterations in thyroid function tests may be observed. Triiodothyronine (T_3) may be depressed in these patients and should not be used in the diagnosis of hypothyroidism.[1] T_4 levels may also be lowered whereas the Free-T_4 values may be elevated.[1,3] The Thyroid Index may provide additional information on the interpretation of the T_4 level. Similar alterations in thyroid function tests may also be observed in patients submitting to surgery.[4]

In these patients the attending physician must attempt a complete assessment of the equivocal clinical and laboratory information, being aware that "normal" ranges for each of the tests may no longer apply. A TSH level three times the upper limit of normal or

TABLE

Thyroxine and Thyroid Index ($T_4 \times T_3$-uptake) Values Determined in Normal Men and Women, In Women Taking Estrogen Medication and in Pregnant Women Expressed as Mean ± Standard Deviation (Number)

	T_4 (μg/dl)	Thyroid Index (Method 1*)	Thyroid Index (Method 2†)
Normal Men and Women	7.22 ± 1.27 (101)	7.19 ± 1.06 (101)	7.15 ± 1.10 (101)
Women Taking Estrogen	11.0 ± 1.3 (15)	8.41 ± 1.41 (15)	7.22 ± 1.55 (15)
Pregnant Women	12.5 ± 2.4 (15)	8.29 ± 1.49 (15)	6.62 ± 1.45 (15)

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*Method 1: T_3-uptake determined as $\frac{\text{Counts on silica — patient}}{\text{Counts on silica — normal}}$

†Method 2: T_3-uptake determined as $\frac{\text{Counts silica}}{\text{Counts serum}}$ and $\frac{\text{uptake patient}}{\text{uptake normal}}$

greater strongly signifies hypothyroidism. A normal or moderately elevated TSH value must be weighed with all other available data (historical, clinical and laboratory). In some instances a Free-T_4 determination may be beneficial; however, one must be cognizant of the elevated Free-T_4 levels in sick people. Should there be any doubt about the interpretation of thyroid function tests, consultation with the Clinical Endocrine Services is advised.

Suggested Protocols for the Use of Thyroid Function Tests

Hypothyroid Evaluation

In hypothyroidism, baseline Thyroid Index and TSH values will substantiate the diagnosis and aid in initiating therapy. T_3-RIA is rarely indicated in the initial or follow-up evaluations of hypothyroidism. With T_4 replacement therapy, the Thyroid Index may indicate a dose that provides normal hormone levels as well as a normal clinical response. It is important to remember that with treatment of hypothyroidism by synthetic thyroxine (T_4) alone, peripheral conversion of T_4 to T_3 will cause T_3 to be present in normal amounts. Another important parameter in regulating the therapy in hypothyroidism is TSH. Since it is generally elevated in hypothyroidism, the return of TSH levels to normal indicates appropriate levels of replacement therapy.

Hyperthyroid Evaluation

With hyperthyroidism, both the Thyroid Index and T_3-RIA will provide initial baseline values and, with treatment using radioactive iodine or anti-thyroid agents, may add important information concerning changes in the patient's thyroid function. For reasons already reviewed, the TSH assay yields no additional information in the daignosis or initial management of hyperthyroidism. If vigorous treatment changes the patient's status from hyper- to hypothyroid, then the above-mentioned management of hypo-thyroidism becomes helpful.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*. Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.

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The anorexic effectiveness of diethylpropion hydrochloride is well documented. No less than 16 separate double-blind, placebo-controlled studies attest to its usefulness in daily practice.[1] And the unique chemistry of Tenuate provides "...anorexic potency with minimal overt central nervous system or cardiovascular stimulation."[2] Compared with the amphetamines, diethylpropion has minimal potential for abuse.

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For prescribing information see opposite page.

The evidence of experience

Since October 1974 when Motrin® (ibuprofen) was introduced in the United States, it has been used by more than 6,000,000 patients with rheumatoid arthritis* or osteoarthritis. Rarely has an ethical pharmaceutical product been prescribed for so many patients in so short a time. In addition, more than 450 studies presenting new data related to Motrin have been published.

The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

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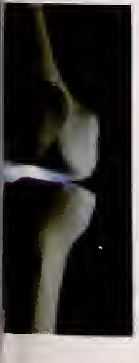
RHEUMATOLOG



Motrin 400 TABLETS mg
ibuprofen, Upjohn

**The confidence that comes from experience—
one more reason to prescribe Motrin.**

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

J-6857-4

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.
Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.
Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

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Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3

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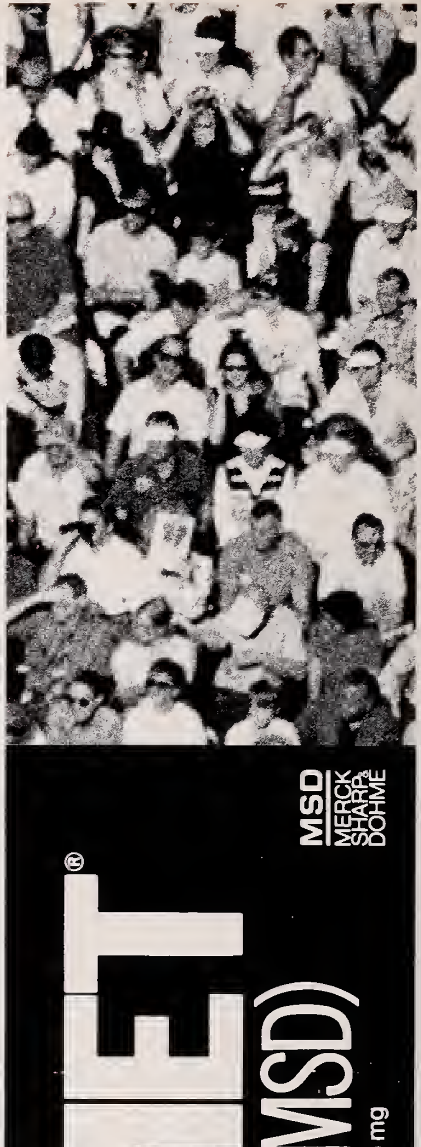

Editorials

Colonoscopic Polypectomy and Beyond

THE VERY EXCELLENT results reported in this article by Drs. Nivatvongs and Goldberg* are impressive statistics. Their series consists of a large group of patients treated over a rather long interval of time with an extremely low complication rate of bleeding, perforation or failed polypectomy. These results should serve as a standard of achievement which *can* be reproduced by others who undertake colonoscopy and polypectomy with the thoroughness and care of Dr. Nivatvongs. It goes without saying, but perhaps it would be wise to reiterate that anyone interested in undertaking endoscopy and especially colonoscopy with polypectomy should be a person who is *gentle* in the handling of tissues and instruments as well as one endowed with *patience*. For without the ingredients of gentleness and patience, one is not destined to be an outstanding colonoscopist; indeed one is destined to be a danger to himself and his patients. The necessary skill and efficiency will develop with experience.

While these results were achieved by an expert who has been a clinical endoscopist for several years, these results *are* reproducible if the physician who wishes to become a capable endoscopist will take the time and trouble to learn from an experienced endoscopist. An interval of formal training during which the student will observe the expert using the instrument is required, and only later will the "student" do the procedures thus ultimately developing excellent technique under the direct guidance of the instructor.

While this is the ideal setting and model for training, some very skilled colonoscopists in this country have developed most of their talents by self-training. However, in today's practice of medicine, one should not undertake a clinical examination as involved and complicated as colonoscopy and polypectomy without significant practice under supervision. This leads to the question of Board certification for performing these procedures. While at the present time there is no such certification, it seems only reasonable to expect that the powers that be (Uncle Sam?) will in the near future require formal demonstration of skill in a qualified training program. Certification of skill is important not only to achieve consistently high quality in training and performance, but also to protect the endoscopist in our ever-increasing environment of malpractice.

The development of endoscopic polypectomy has given the medical profession the ability to remove polyps "nonoperatively" and should discourage the practice of colotomy and polypectomy or exploratory laparotomy and colotomy with resection for lesions of the colon without an attempt preoperatively at colonoscopy and polypectomy by a competent endoscopist.

Just as vital to the success of endoscopy and polypectomy procedures is the setting in which these procedures take place. The ideal setting is a fully developed endoscopy unit staffed by thoroughly trained technicians or nurses who are fully aware of the instrumentation, the care and repair of the instruments, and the proper techniques in assisting the endoscopist. Just as it is true that the assistants to the surgeon in the operating room can make or break him, the nursing assistants to an endoscopist can either create havoc with the procedure or make it a smooth, safe experience.

How can we utilize the colonoscope to even greater advantage in the future? The whole question of polyp surveillance for malignancy is central in the prevention and cure of colon and rectal cancer. We know that 85% of polyps and malignancies in the colon and rectum occur from the splenic flexure of the colon to the anus. This area of the bowel in most cases is within the range of the "long" colonoscope and the newly developed "short" 60 cm fiber colonoscope. Perhaps the old saw about the annual procto exam will graduate to a philosophy of screening for polyps and malignancies by annual hemoccult examinations combined with an extended endoscopic examination at least to the splenic flexure performed every two or three years. It has been recognized lately that the use of the 60 cm flexible fiberscope can be an office or an out-patient procedure that will allow excellent visualization of the colon to the splenic flexure. This exam takes five to ten minutes in the hands of an experienced endoscopist.

Further discussion centers around what to do with the small (less than 0.5 cm) sessile polyps that are seen on endoscopy. The incidence of malignancy is almost nil. Many of these polyps are of the hyperplastic variety which show *no* tendency toward growth or malignant change. However, many authorities would

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*See page 197.

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suggest that biopsying these polyps is necessary. The reason for biopsy is to know whether or not these are adenomatous polyps which would have a tendency to grow and perhaps develop malignancy with time.

An established practice today which should receive even greater attention in the future is the screening for the presence of dysplastic changes or frank malignant changes in patients with chronic ulcerative colitis of longstanding duration. Morson and Pany[5] have long since delineated the dysplastic micro-pathologic changes that pre-date clinical cancer of the colon in these patients. The beneficial use of the colonoscope to find these patients *before* frank carcinoma occurs is obvious.

An important factor is the definite avoidance of any aspirin compounds or other ''blood thinners'' that the patient may be on and may *not* give a good history regarding. Elderly patients frequently are on aspirin-containing compounds but do not know it and a thorough questioning of all their medications is important. The performance of endoscopic polypectomy while the patients are on these compounds would lead to the risk of massive hemorrhage following biopsy or polypectomy.

It is also still important to stress the need for a quality barium enema or air-contrast barium enema as a complement in finding pathology of the colon. While not all barium enemas and not all colonoscopic examinations will delineate pathology, by combining the two examinations there is nearly 100% identification of lesions. One should also stress the importance of ''rigid'' procto examination and anoscopy in dealing with the more common varieties of anorectal pathology such as internal hemorrhoids, detecting rectal mucosal prolapse and the treatment of these conditions in the office.

The routine use of fluoroscopy is rarely indicated. Two new techniques have been discussed in the literature which may aid in the preparation and performance of colonoscopy. The utilization of whole gut irrigation (gastric lavage utilizing Maxalon® as a gastric emptying stimulant) has been reported in the British literature lately. Excellent preparation of the colon has been reported within three to four hours time. The proviso is that the patient has a stable cardiovascular system and can tolerate a large volume irrigation in a short period of time. This type of bowel preparation has obvious advantage over the three day preparation as suggested by Dr. Nivatvongs and others as well as not requiring the patient to be on a stringent diet.

Another possible use of colonoscopy is the intraoperative utilization of this device to assist the surgeon in assessing pathology. The patient is prepared for colon surgery and anesthesized in the usual fashion. The colonoscope is then passed per anus by the lower examiner while the abdominal examiner can aid the endoscopist by manipulating the instrument and allowing a more complete examination with no patient discomfort. This technique is being developed by Dr. John Alexander-Williams of Birmingham, England.

Conclusions: The results reported in this article are excellent and serve as a standard for all of us to try to duplicate. We consider the ideal situation to be one where the endoscopist enjoys a high volume of work, thus allowing a high achievement of skill and performance. In addition, an excellent assistant, technician or nurse with the proper knowledge of all the instrumentation involved and the care of the same is mandatory for the successful and safe use of this instrument.

Perhaps the ''long'' colonoscope and/or the 60 cm flexible fiberscope utilized in association with screening for occult blood in the stool will have greater importance in the future in screening for and detecting colonic polyps and colonic malignancy at an earlier stage.

Frederic D. Nemer, M.D.
Minneapolis, Minnesota

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RH Isoimmunization

THE RESULTS OF A Rh isoimmunization prevention program in a community hospital are reviewed by Dr. A. C. Aufderheide* of the Department of Pathology of the University of Minnesota, Duluth School of Medicine.

The study included the records of all women receiving anti-D serum from July 1968 to December 31, 1975. The emphases of the study were: (1) breakdown of program operation, and (2) frequency of sensitization to D antigen among women who received anti-D serum. The program was extremely efficient. Regarding the efficacy of the program, of the 9,800 women delivering babies during the study, 807 received anti-D serum, but only 125 of these women had subsequent pregnancies with a total of 151 Rh-positive infants. Of these 151 pregnancies, there were two instances of maternal sensitization. This failure rate corresponds with reports from other studies.

Tovey and Robinson[1] report a failure rate of 1-2 percent after anti-D immunoglobulin prophylaxis. They point out that these failures fall into two main patterns. The first relates to women who develop antibody late in a subsequent pregnancy, probably due to fetomaternal hemmorhage early in a subsequent pregnancy, and the second relates to when the antibody is detected in a subsequent pregnancy at the first antenatal visit and persists throughout the pregnancy. They postulate that this failure may be due to an insufficient dose of anti-D or more likely that the patient was already sensitized when the anti-D was given.

Freda, Gorman, et al.[2] state that all Rh-negative women who are at any risk of becoming sensitized to Rh must be protected with immune globulin whether they have had a term pregnancy, an abortion, or an accidental transfusion with Rh-positive blood. When serologic tests are questionable, withholding Rh immune globulin is not considered proper since it will not cause harm in mothers already sensitized.

Bowman, et al.[3] interestingly report on a clinical trial of a single administration of Rh immune globulin at 28 weeks gestation. This was effective in preventing antenatal isoimmunization. A second injection is given after delivery. This method is now standard throughout the Province of Manitoba.

Hreidar Agustsson, M.D.
Minneapolis, Minnesota

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*See page 181.

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Urologic Ski Injuries

AS MENTIONED IN Hildreth's paper*, winter sports injuries are becoming more frequent as increasing numbers of people are taking up skiing in our area. Because of their anatomical function, the genitourinary organs are less likely to be injured than the extremities. Nevertheless, blunt injuries from falls and collision and impaling trauma from poles and skis may result in significant urologic lesions as mentioned in the article. All of the reported injuries were the result of alpine (downhill) skiing. I am not aware of any serious urologic injuries in nordic (cross-country) skiing in our area but, as the sport becomes more popular, Murphy's law will hold true. Gross or microscopic hematuria, undoubtedly, is the most frequent indication of urologic injury and should be investigated thoroughly as listed in the article. The association of the other injuries is high and the possibility of a minor injury causing trauma in a diseased kidney should be kept in mind. Prompt and specific management will result in less morbidity and preservation of function.

The authors are to be commended for their timely report.

Gordon W. Strom, M.D.
Minneapolis, Minnesota 55435

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*See page 155.

Minnesota Medical Association

General Management Guideline for the Alcoholic and Other Chemically Dependent

THOMAS G. BRIGGS, M.D.*

The following suggestions are offered in helping the physician manage the chemically dependent. A majority of these patients will be dependent on alcohol. There may be duodependencies with the sedatives, minor tranquilizers, narcotics, amphetamines, street drugs, and others.

1. Include a Detailed Drinking History in Routine Physical Exams in the Office and Hospital

Simple questions such as: "Has alcohol or other chemicals ever been a problem in your life?", "Have friends or relatives ever been concerned with your use of alcohol?", "What is the most you have drunk in 24 hours?", "Have you ever been concerned about your drinking or use of other drugs?"

2. Don't Moralize with the Alcoholic or Other Chemically Dependent

They have usually had this at home. Encourage them as much as possible. Point out that this is a treatable illness and with an honest desire to quit and the support of self help groups such as AA, they can do it.

3. Be Honest to Develop Trust

Don't use deceptive tactics or what you say and do in the future will be less productive or suspect.

4. Arrange AA Contact Yourself

If left to the patients, they will often tell you they will follow through but seldom do. By taking this option away, you will help ensure their participation. The same holds true for Alanon which is designed for the spouse of the alcoholic.

If you don't know any AA members in your practice, request they identify themselves to you by a note on your bulletin board or simply call the nearest AA office. They will gladly take your patient to their next AA meeting.

5. If You Are Not Interested in Treating the Alcoholic, Get Them to Someone Who Is

I am continually amazed about the number of doctors who complain about the alcoholics in their practice, and yet they jealously hoard them as if there weren't enough to go around. The AMA manual on alcoholism points out that "we tend to deny what we don't know or understand." The average M.D. received less than two hours in four years of medical school on the #3 illness, the 2-4-3 syndrome. Consider visiting an AA meeting or visit an inpatient treatment center.

But for those that would rather not be involved, get your patients into the hands of someone who is.

6. Be Cautious in the Use of Alternate Chemicals

(The so called minor tranquilizers, librium, equanil, valium, etc., barbituates and other sedatives, pep pills, narcotics, and other mood altering chemicals.) Librium and valium can be valuable in the withdrawal phase but these and the others mentioned are contradicted in the wet and dry alcoholic and others that are chemically dependent.

7. Use Other Members of the Treatment Team Freely

AA members, treatment center counselors and others experienced and interested in handling the alcoholic can and should be members of the treatment team. This disease lends itself well to the team approach and relieves the physician of much of the time commitment that most of us would be unable to fill.

8. Don't Tell a Patient He/She Is Not an Alcoholic if You Are Not Sure

The chemically dependent can be excellent "con" artists and fool even an experienced clinician. Substantiate a story with a reliable significant other usually a spouse but may be other relatives, friends, or boss. By assuring an alcoholic "you don't seem alcoholic to me," he will use your position of authority to assure others that "a doctor said I was clean," and significantly delay treatment.

9. Stuttering Stop

Don't give up on an alcoholic anymore than you would on a diabetic that didn't strictly adhere to his diet. Reeducate. Many good sobrieties had this stuttering stop.

10. The Power of Petition

Minnesota physicians can hold a patient in a hospital for 72 hours, exclusive of weekends and holidays, if the physician is concerned that the patient will be a danger to himself/herself or others if they leave prior to treatment. These blanks are available from your probate court for this use. Used with family support, it is a very effective tool to coerce the patient into treatment.

---

*Medical Director, St. John's Hospital Chemical Dependency Treatment Center, St. Paul, and Chairman, Committee on Alcohol & Drug Abuse, MMA

Almost all patients enter treatment programs with some form of pressure even though they will tell you they entered voluntarily. What they don't tell you is that if they don't complete inpatient treatment they will (1) get 30 days, (2) lose their job, or (3) lose their spouse. Results from this form of therapy are very rewarding.

11. It's Not How Much They Drink But What It Does to Them

An experienced clinician can be misled by the amounts an alcoholic drinks.

One of my patients, a 19 year old woman could hold only three beers a day. She became extremely intoxicated on that amount and on admission to our unit had a record of ten D.W.I. It severely interferred with her interpersonal relationships. She was extremely frustrated by the fact that she was never able to drink more or keep up with others. It was difficult for her to accept that she could be an alcoholic on three beers a day at the most.

Another example is a lady school teacher who drank but a pint of vodka a week. It was her pattern of drinking and what it did to her that gave us the diagnosis (along with other supporting evidence). On Thursday, her day off, she would become snapped up on her pint of vodka.

At the other extreme was a 25 year old man who drank two quarts of vodka a day plus one case of beer.

So it's not just the amount of alcohol consumed but rather what that amount does to them.

12. Alcoholics Will Frequently Respond to A Firm but Kind Compassionate Physician

Don't just treat his liver — treat the whole patient.

13. Be Patient

Recovery may be slow but treatment is very rewarding. As one alcoholic said, "just let us know you care."

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Index to Advertisers

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Anderson, C. F. Co. 166

Army Reserve 174

Beltone Electronics Corporation 165

Burroughs-Wellcome Co. 180, 184

Classified Advertising 206

Fidelity Professional Services, Inc. 144

Hempel Financial Corporation 174

Lilly, Eli & Co. 146

Mead Johnson Pharmaceutical Division 157, 158

Medcalf Orthopedic Appliance Co. 192

Medical Protective Company 144

Merck, Sharp & Dohme 170

Merrell-National, Inc. 166, 167, 190, 191, 192

Metropolitan Medical Placement 186

Minnesota Medical Association 200, 208

Pfizer Laboratories 172

Roche Laboratories . . . . . . Cover 2, 178, 179, Covers 3,4

Smith, Kline & French 189

United States Air Force 204

Upjohn Company 168, 169, 170

Warner-Chilcott Co. 142

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Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxid HCl and/or clidinium Br.

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***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment, blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

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In treating irritable bowel syndrome*

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*Librax has been evaluated as possibly effective for this indication.
Please see brief summary of prescribing information on preceding page.

EMPIRIN® COMPOUND
c̄ CODEINE

Each tablet contains: aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛), (Warning—may be habit-forming). CIII

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Special Article

RH Isoimmunization Prevention Program in a Community Hospital

ARTHUR C. AUFDERHEIDE, M.D.*

9800 routine deliveries in a community hospital over a period of 91 months were monitored and an anti-D serum administration program effected for the prevention of isoimmunization to the Rh (D) antigen. The administrative features of the program functioned well. 807 mothers received 913 vials of commercially marketed anti-D serum. 124 of these had 151 subsequent pregnancies with Rh positive infants. In spite of this program, two mothers became sensitized to the D antigen and delivered infants moderately affected by hemolytic disease of the newborn. One of these probably represents an instance of fetomaternal hemorrhage occurring during the midportion of the gestational period, while the other most probably represents a "massive" fetomaternal hemorrhage at the time of delivery undetected by the monitoring method in use at that time. Methods to detect "massive" fetomaternal hemorrhage should probably include one which is more sensitive than the "anti-D cross match" technique provided with each vial of commercially produced anti-D.

IN 1968 THE MEDICAL staff of St. Mary's Hospital in Duluth, Minnesota, charged the hospital Department of Pathology with developing and implementing a program of Rh isoimmunization prevention. The results of this program from 1968 to 1975 are presented in this report.

The Prevention Program

The red blood cell (RBC) group and type of all women admitted to the hospital's obstetrical floor are determined on admission, as well as of babies born to Rh negative mothers. A direct anti-globulin ("Coombs") test (AGT) is carried out on RBC of all newborns. AGT is carried out on the mother's serum to detect the presence of anti-D antibodies. When an Rh negative mother with no evidence of sensitization to the D antigen delivers an Rh positive infant whose cord RBC also fail to reveal anti-D antibodies, the attending physician is notified by the obstetrical floor nurse that the patient is a "candidate" for anti-D administration. Upon receipt in the laboratory of a physician order to proceed with the program, a vial of commercially available anti-D serum (RhoGam (R) or Gamulin (R)) is selected and a sample of maternal blood is "cross matched" with a 1:1000 dilution of such serum. More recently a "microscopic Du"[1] procedure is also carried out on the maternal blood sample to detect possible massive fetomaternal hemorrhage. If these procedures are negative, the anti-D serum vial lot number is recorded and then sent to the floor where the nursing staff injects it intramuscularly into the patient. Failure to receive a physician order within 72 hours of delivery results in notification of the hospital pathologist who contacts the attending physician directly to be certain that his failure to order anti-D administration is his exercised option and not merely the consequence of an informational flow breakdown. All laboratory procedures were carried out as detailed in "American Association of Blood Banks Methods and Procedures," 1974.†

The Study

The hospital charts and office records of all women receiving anti-D serum between July 1, 1968 (initiation of the program) and December 31, 1975 were reviewed. If subsequent pregnancies terminated in some other hospital, those records were procured and reviewed.

Items of study interest included the following:

(A) Evidence of program operation breakdown:
  1. Time interval between delivery and anti-D serum injection
  2. Failure to notify physician of a patient's candidacy for anti-D serum administration.

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Address reprints to: Department of Pathology, University of Minnesota, Duluth, School of Medicine, 2205 East 5th Street, Duluth, Minnesota 55812.

†Publisher: J. B. Lippincott.

See editorial, page 175.

(B) Frequency of sensitization to D antigen among women who received anti-D serum.
(C) Detection of potential or actual unexpected problems.

Results

The Table identifies the numerical information extracted from the study.

Discussion

Operation of Administrative Portion of the Program.

The fact that the laboratory and nursing staff consists of a small number of dedicated and highly competent persons may be a significant factor in the smooth operation of the program. No instances of communication failures were identified. The usual reason for failure to administer anti-D serum to a mother who was serologically otherwise eligible was patient refusal because of planned postpartum sterilization. With three exceptions all sera were administered within 72 hours of delivery. The first of these three exceptions was the first patient in the program. She delivered six days before the commercially marketed serum first became available. The second exception was a patient with a ruptured tubal pregnancy, undiagnosed before surgery, who received the serum immediately postoperatively, but 76 hours (by history) following tubal perforation. The third exception was a patient with a technically complex problem at delivery requiring considerable laboratory study before defining the situation; this delayed administration of serum to the sixth postpartum day. The study identified no reason to alter the administrative aspects of the program.

Immunization "Failures"

An immunization "failure" is defined in this study as any woman receiving anti-D serum who later demonstrates evidence of sensitization to the D antigen. The program as defined above does not include postpartum serologic evaluation to determine whether sensitization to the D antigen occurred in spite of anti-D administration. Among the numerous reasons for this is the difficulty of identifying such sensitized patients serologically. About 60% of these sensitized women have antibody levels at six months postpartum too low to be detectable. Their sensitized status becomes apparent when these antibody levels are raised to an easily identifiable level by an antigenic stimulus in the form of a subsequent pregnancy with another Rh positive fetus.[2] Assessment of success or failure can, therefore, be made with conviction only among those women receiving anti-D serum who had at least one subsequent pregnancy with an Rh positive fetus and were studied serologically at that time. Of the 9800 women delivering babies during the study interval, 807 received 913 vials of anti-D serum, but only 125 of these women had subsequent pregnancies with a total of 151 Rh positive infants. Of these 151 pregnancies, there were two instances of maternal sensitization to the D antigen. A brief description of these patients follows:

Case Reports

"Failure" #1

A 29-year-old Rh negative woman delivered three successive Rh positive infants. After the first was delivered vaginally and uneventfully in May, 1968, she was given one vial of anti-D serum six days postpartum when the first available shipment of this material arrived locally. Fifteen months later she delivered her second child. No evidence of sensitization to D antigen could be identified during pregnancy (serum anti-D tests performed during each trimester), nor at delivery, so one vial of anti-D serum was administered 22 hours postpartum. Her third delivery occurred in January, 1971, 19 months after the second. During this pregnancy she first visited her physician at the end of her first trimester, at which time a "screening" test for anti-D antibodies (indirect AGT) in her serum was negative. When this test was repeated at the start of her third trimester it was positive; anti-D antibody was present in a titer of 1:64 ("Coombs"). Several amniocentesis studies suggested mild fetal hemolysis (borderline zone I-II results)[3] and elective induction of labor at 38 weeks gestation resulted in a 3035 gram Rh positive infant (Group 0, c̄ De/c̄). Cord blood revealed a hemoglobin level of 18 gm%, a total bilirubin level of 3.6 mg% and a positive direct AGT. The baby's total bilirubin level peaked at 25 mg% on the fifth postpartum day, then gradually declined without exchange transfusion.

The cause of the "failure" to prevent sensitization to the D antigen in this patient was probably the result of an undetected fetomaternal hemorrhage occurring during the second trimester of the last (third) pregnancy. No abortions, menstrual irregularities or infusion of blood or blood products had occurred at any time. The six day delay in administration of anti-D serum following the first delivery in 1968 might be suspect, but is an improbable cause because the second pregnancy with an Rh positive infant (the most potent known stimulus to antibody production in an already sensitized, but

TABLE

Numerical Information Abstracted from Chart Review

Study Interval: June 1, 1968 through December 31, 1975 (91 months)

Deliveries at SMH* During That Period	**9800**
Rh Negative Women Receiving Anti-D	**807**
Vials Anti-D Administered	**913**
Women With Rh Positive Pregnancies Subsequent to Anti-D Administration	**124**
Rh Positive Pregnancies These 124 Women Had	**151**
Anti-D "Failures"	**2**
Women With 2 "Protected" Pregnancies	**16**
Women With 3 "Protected" Pregnancies	**2**

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*SMH: St. Mary's Hospital, Duluth, Minnesota serologically undetectable mother) failed to reveal the presence of anti-D at that time. Indeed, even the second pregnancy seems to have failed to immunize her since no antibody was found at 12 weeks gestation in the third pregnancy (D antigen has been identified in RBC of feti of five weeks gestation). The most probable explanation, thus, would appear to be that the sensitization identified at 24 weeks gestation was the result of a sensitizing fetomaternal hemorrhage occurring between the time of these two measurements; i.e., during the second trimester rather than the much more common occurrence at the time of delivery.

"Failure" #2

In November, 1973, this 23-year-old Rh negative woman was uneventfully delivered vaginally of a normal Rh positive infant. When no evidence of sensitization was detected she was given one vial of anti-D serum 52 hours after delivery. She had no serologic studies until the delivery of her second child, an Rh positive infant, 16 months following the first. At that time anti-D antibody was present in her serum. Cord blood RBC were Group 0, CD e/c̄ e, hemoglobin level 11.3 gm%, total bilirubin level of 10.4 mg%, and a positive direct AGT. When the infant's bilirubin level reached 25 mg% exchange transfusion was carried out with subsequent decline in bilirubin level.

In view of the absence of abortions, menstrual irregularities or infusion of blood or blood products, sensitization most probably occurred as the result of either fetomaternal hemorrhage of a degree in excess of that "protected" by one vial of anti-D serum or as a result of fetomaternal hemorrhage during the second pregnancy. The latter can not be evaluated because of the absence of serologic studies during the second pregnancy, but it is a rare occurrence (even though "Failure" #1 outlined above seems to be just such an example). More likely massive fetomaternal hemorrhage occurred at the first delivery, undetected by the "anti-D cross match" method then used, and consequently inadequately treated.

One vial of anti-D serum contains 300 micrograms of anti-D antibody with physical and chemical characteristics such that it could be expected to "block" the sensitizing effect of about 15 cc of packed fetal red blood cells (or about 30 cc. of whole fetal blood). This seems to occur in about 0.3% (three in 1000) of normal deliveries.[2] Thus, about 3 such instances could be expected to have occurred among the group studied here. In fact, two such episodes were identified (one with an estimated 40 cc of fetal cells circulating in the mother and the other with about 25 cc). But, the "anti-D cross match" technique used in these cases, as well as in "Failure" #2 described above, is known to detect only about 2/3 of fetomaternal hemorrhages of 15 cc quantity.[1] The "microscopic Du" method is much more sensitive (detecting about 90% of such hemorrhage) and the Kleihauer hemoglobin F smear technique is believed to approach 100% detection of such fetomaternal hemorrhage in excess of 15 cc.[1] Depending on cost considerations, one of the latter methods may be a more desirable routine method to monitor such "massive" hemorrhages requiring more than one vial of anti-D serum to provide adequate protection against isoimmunization.

Two failures to prevent Rh isoimmunization in these 151 instances of pregnancies, with an Rh positive fetus following anti-D serum administration at the time of previous delivery (1.3%), is about equal to the experience of large groups in other parts of the country (1.5%).[2]

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1. Polesky H: Detection of fetomaternal hemorrhage: an evaluation of serological tests related to Rho (D) immune globulin (human). Transfusion 11:162, 1971.
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3. Liley AW: Liquor amnii analysis in management of pregnancy complicated by rhesus sensitization. Amer J Obstet Gynec 82:1359, 1961.

Minneapolis Children's Health Center
Pediatric Grand Rounds

MARCH 13
"Physical Aspects of Alcoholism"
Dr. Gerardo D. Neuwirth, North Suburban Pediatrics, Anoka, MN

MARCH 20
Department of Medicine Meeting
Dr. David R. Brown, Chief of Medicine

MARCH 27
"A Spectrum of Staphylococcal Disease in Pediatrics"
Presenters: Dr. Scott Giebink, Dr. Mace Goldfarb and Dr. Dale Dobrin
Minneapolis Pediatricians
and Dr. Lee Prewitt, Radiologist MCHC

A reminder

ZYLOPRIM
(allopurinol)
100 and 300 mg scored Tablet

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age: Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

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Rheumatology Corner

Diagnosis of Rheumatoid Arthritis

JAMES REINERTSEN, M.D.*

THE FULLY DEVELOPED, advanced case of rheumatoid arthritis (RA) is easily recognized. During the first months of illness, however, diagnosis is a clinical challenge, since many disorders mimic RA (Table). Recognition of RA during this phase depends primarily on careful and repeated observations, often for many months, before a definite diagnosis can be established. The prudent physician will recognize that "rheumatoid arthritis" carries serious psychological and insurance implications for the patient and can delay recognition and treatment of other disorders. It is good practice to avoid a premature diagnosis of "RA," and to label early cases as "polyarthritis, etiology unknown," until the diagnosis is no longer doubtful.

Even during the first months, diagnosis is easy in many cases, Typically, a middle-aged woman will present with the insidious onset of vague pain and stiffness in wrists, metacarpophalangeal and proximal interphalangeal joints, elbows, shoulders, and neck, often followed by involvement of metatarsophalangeal joints, ankles, and knees. Over several months, persistent and symmetric swelling appears. Pain is increased after prolonged immobility. Fatigue is prominent, but fever and other systemic symptoms are not.

Examination will reveal pain on motion and palpation of involved joints accompanied by subtle but definite periarticular soft tissue swelling. The proximal interphalangeal joints characteristically develop a spindled appearance. As the disease evolves, it can steadily progress, remit and relapse, or, in a few cases, enter a sustained remission. In later stages, typical hand deformities occur, and nodules develop in 20 percent of patients.

Tests for rheumatoid factor are often negative early but within two years will be persistently positive in 70 to 80 percent of adult cases. Seronegative patients should be closely observed for evidence of other causes of arthritis. An elevated sedimentation rate adds weight to the diagnosis of RA but is not always present. Radiographs will eventually show erosion of joint margins in virtually all patients with RA; if erosions are

TABLE

Disorders that May Mimic Various Presentations of Rheumatoid Arthritis

1. Typical Presentation of RA	II. Atypical Presentation of RA
Depression	A. Acute polyarthritis
Viral arthritis (rubella, hepatitis)	
Systemic lupus	Systemic infection
Scleroderma	Drug reaction (serum sickness)
Vasculitis	Collagen disease
Hyperthyroidism	Polyarticular gout
Hypothyroidism	
Inflammatory osteoarthritis	B. Chronic mono/oligoarthritis, seronegative
Infection, such as SBE	
Hypertrophic pulmonary osteoarthropathy	Infection
Sarcoidosis	Osteoarthritis
Multicentric reticulohistiocytosis	Crystal-induced arthropathy
Behcet's syndrome	Spondyloarthropathy (Reiter's, psoriasis, inflammatory bowel disease, spondylitis)
Hyperlipidemia	
Amyloidosis	
	C. Palindromic rheumatism
	Gout
	Pseudogout
	D. Extra-articular disease

---

*Department of Internal Medicine, St. Louis Park Medical Center, Minneapolis, Minnesota.

Before joining the St. Louis Park Medical Center, Dr. Reinertsen was an associate physician with the National Institutes of Arthritis, Metabolism, and Digestive Diseases (Arthritis and Rheumatism Branch), U.S. Public Health Service, Bethesda, MD.

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absent after two or more years of disease, the diagnosis of RA should be seriously questioned.

In contrast to the typical case above, several other early presentations of RA present diagnostic problems.

Such presentations include:

1. Acute fulminant polyarthritis: Patients may be bedridden within weeks. The absence of high fever is useful in distinguishing RA from infections, collagen disease, and vasculitis.
2. Chronic mono- or oligo-articular arthritis, often seronegative: This type of RA is more common in children. In mono-arthritis at any age, infection should always be excluded, by open synovial biopsy if necessary. In many patients, careful history and examination will eventually reveal psoriasis, Reiter's syndrome, spondylitis, or inflammatory bowel disease.
3. Palindromic rheumatism: Acute episodes of nondeforming mono- or oligo-arthritis can precede RA for years. Gout, pseudogout, and infection should be excluded.
4. Extra-articular disease: Rarely, the initial manifestation of RA is pleural effusion, pericarditis, interstitial pulmonary fibrosis, Felty's syndrome, or other systemic complication of RA. Under these circumstances, the presence of high titre rheumatoid factor and/or typical rheumatoid nodules on biopsy will indicate the correct diagnosis. Rheumatoid serosal effusions often have a very low glucose content.

Rheumatoid arthritis is not difficult to diagnose in most cases. In the first weeks of illness in seronegative patients and in atypical presentations, the clinician is challenged to make the correct diagnosis early enough to initiate treatment which can potentially delay or prevent joint destruction and yet avoid a premature, harmful misdiagnosis of ''rheumatoid arthritis.''

MMA Annual Meeting

RAMSEY COUNTY MEDICAL SOCIETY is hosting the 1979 MMA Annual Meeting. MMA President Dr. Robert Flom enthusiastically invites your attendance. He and his colleagues from St. Paul are anxious to welcome you May 16-17-18 at the Radisson St. Paul Hotel. Local Arrangements Chairman is Dr. John Burns. Scientific Exhibits are reviewed by Dr. Luigi Taddeini. Golf Tournament coordinators are Dr. Thomas Nichols and Dr. David W. Anderson. First Annual MMA Foot Races are planned by Dr. Edward Hanton and Dr. Lowell Lutter. Tennis Tournaments are under the direction of Dr. Leonard Levitan and Dr. Richard Graham. Preregister now and come to St. Paul for the 1979 MMA Annual Meeting.

Continuing Medical Education

Gillette Children's Hospital

The Cole-Chatterton Memorial Symposium on Lower Extremity Disorders in Children will be held May 4-5, 1979 at Gillette Children's Hospital, regional center located in St. Paul, Minnesota for children with neuro-muscular-skeletal disorders.

The Symposium is designed for orthopedists, orthopedic residents, pediatricians, family physicians and allied health personnel.

AMA Category I Continuing Education credits will be given. $25 fee. For further information write to Phyllis Weigum, Medical Education, Gillette Children's Hospital, 200 University Avenue East, St. Paul, Minnesota 55101.

University of Minnesota

The Department of Surgery of the University of Minnesota Medical School will present its 43rd Annual Surgery Continuation Course June 13-16, 1979 at West Bank Auditorium, University of Minnesota campus. The theme for this year's course is ''Hepatic, Biliary and Pancreatic Surgery.

Emeritus Editor's Soliloquy

"We'll See You in A Moment"

My very dear Medical Society; or (lest I get shoved into the bureaucratic limbo of no return) Distinguished Chairman of the Board of Medical Examiners; or Esteemed Chairman of the Council; or Your Eminency, Mr. President; or Honorable Messrs Whosoever:

I present this treatise not for myself alone but also for all my colleagues who have attained senior-citizenship status in the practice of medicine. We have now pursued our humanitarian profession for more than half a century; we have paid our dues and our license fees; we have abided by the rules of Esculapius and have honored the Hippocratic oath; in short, we have been conscientious practitioners, dedicated to our profession. Only now are we beginning to note twinges of fatigue at the close of a busy day with never so much as the luxury of a midday siesta.

Now we are asking the Powers that be: Are our licenses to practice the noble art and science of medicine to be revoked if we discontinue practice? Or if we do not attend to our Brownie points? Having heard a sinister rumor to that effect, we are inquiring about the source and authenticity of that rumor.

Abrogation of a doctor's license is generally regarded as tantamount to unethical conduct on his part — a fall from grace, with a subtle implication, insinuation, or innuendo of treason or heresy. We have never engaged in unprofessional conduct, and we would resent being equated or identified with those practitioners who have violated their commitment and thereby forfeited their privilege to practice.

In fact, does not our Society permit half a dozen scoundrels to practice as long as they pay their dues, thereby establishing lip service to the high standards and ideals of the profession?

One senior doctor acquaintance of mine from Georgia showed me his gold-engraved lifetime membership card, relieving him of the payment of all dues and burdensome responsibilities, yet permitting him to practice as long as he lives. He is proud of this card, happy to continue serving, and loyal to his local medical society.

Revocation of our licenses would appear to brand us "seniors" as non-doctors, as has-beens, canceling out our long and meritorious service. Does even the lowliest organization thus penalize its retired members?

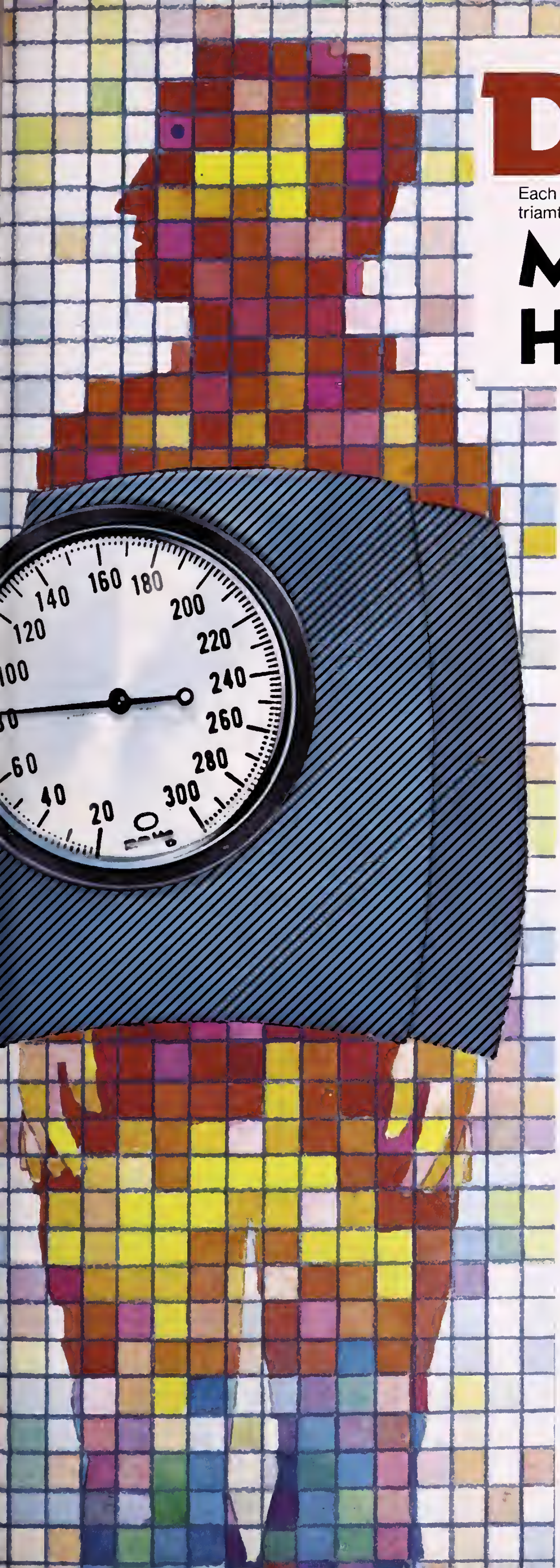
Even though we might prefer to terminate practice, at retirement it would be difficult to face up to the humiliating psychic trauma that loss of licensure would entail. It would be like one's francise abolished, one's citizenship invalidated. It would seem like exile to a Gulag archipelago!

Must we be sacrificial goats to an obdurate and archaic bureaucracy just because we have reached a certain chronologic age? Must we be relegated to oblivion, consigned to outer darkness?

Or will it take another generation of ineffectual committees and unproductive meetings to solve the dilemma?

As the time-clock of eternity marches on, in a mere moment you-all "Juniors" will have arrived at the same impasse. Will that be your choice then? Think it over carefully. Ponder it wisely.

Carl O. Rice, M.D., Ph.D.
Editor Emeritus



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> This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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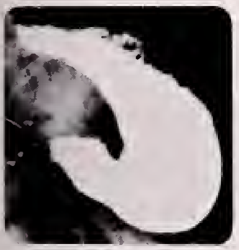
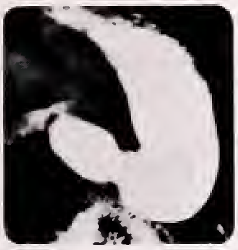
. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Brief Summary

INDICATIONS
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS. In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention, blurred vision and tachycardia; palpitations; mydriasis; cycloplegia, increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia, nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage Bentyl 10 mg capsule and syrup: *Adults.* 1 or 2 capsules or teaspoonfuls syrup three or four times daily *Children* 1 capsule or teaspoonful syrup three or four times daily *Infants:* ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults:* 1 tablet three or four times daily Bentyl Injection: *Adults* 2 ml. (20 mg.) every four to six hours intramuscularly only NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978

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Fracture Conference

Snowmobile Injuries in Children

HAMLET A. PETERSON, M.D.*, TIMOTHY C. FITZGIBBONS, M.D.† and MICHAEL A. ARATA, M.D.†

Dr. Hamlet A. Peterson:

An abundant amount of snow has accumulated this year, and along with this increase we have noted an increase in the number and severity of pediatric injuries associated with snowmobiles. This fracture conference concerns snowmobile injuries in children.

Report of Cases

Case 1

Dr. Timothy C. Fitzgibbons:

A 10-year-old boy was driving his snowmobile around the barnyard while being chased by his eight-year-old brother on another snowmobile. The patient ran into a tree and immediately noted pain and swelling of his left wrist and right knee. He was taken to the emergency room. The neurovascular status of all extremities was satisfactory, but he had notable effusion of his right knee and swelling of his left wrist. The following roentgenograms were made (Figure 1).

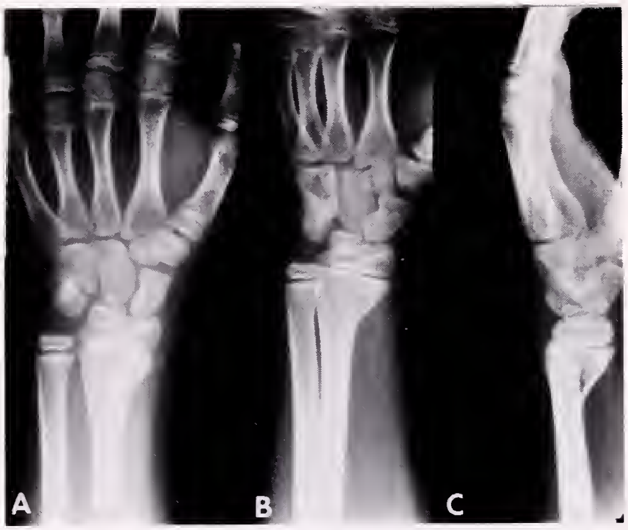

Fig. 1 (Case 1). Left wrist after snowmobile injury. (A), Posteroanterior view. (B) Oblique view. (C) Lateral view.

Dr. Peterson:

The roentgenograms of the knee were negative. Dr. Burkhart, would you comment on the roentgenograms of the left wrist.

Dr. Stephen S. Burkhart:

There appears to be a Salter-Harris type 2 fracture of the distal left radius with volar displacement.

Dr. Peterson: How would you manage this?

Dr. Burkhart: I believe closed reduction and plaster immobilization would be satisfactory.

Dr. Fitzgibbons:

Fifty milliliters of blood was aspirated from the right knee, and on examination, the patient was believed to have a partial tear of his right medial collateral ligament. The knee was immobilized in a cylinder cast. The left wrist was manipulated and held with a long-arm cast (Figure 2). The patient is now recovering from his injuries.

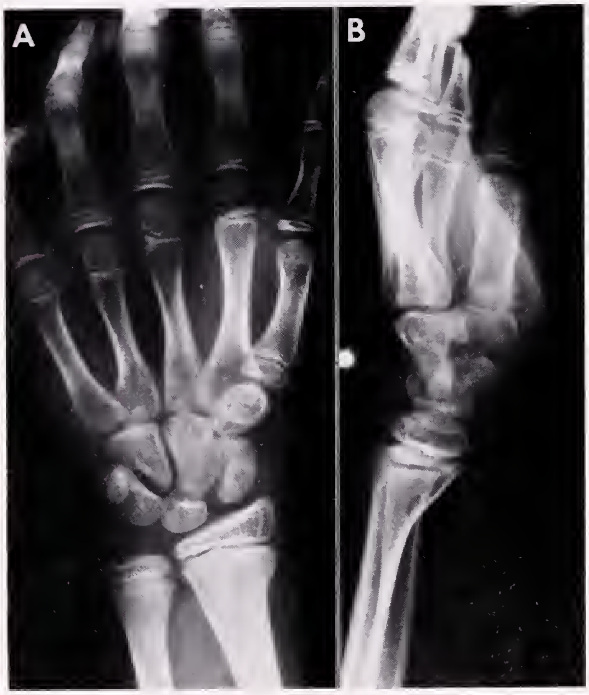

Fig. 2 (Case 1). Wrist after closed reduction. (A) Anteroposterior view. (B) Lateral view.

---

*Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

†Resident in Orthopedics, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.

Fracture Conference, March 8, 1978.

Reprint address: H. A. Peterson, M.D., Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

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Dr. Peterson:

This case illustrates poor judgment on the part of the parents, who bought two snowmobiles and allowed their eight-and 10-year-old sons to drive them.

Case 2

Dr. Fitzgibbons:

The next patient is a seven-year-old boy who was attempting to push his snowmobile from behind when his right foot became trapped in the moving snowmobile track. When examined in the emergency room, he had extensive loss of skin and soft tissue from the lateral side of his right foot and ankle, and the ankle and subtalar joints were exposed. The following roentgenograms were made (Figure 3).

Dr. Peterson: Dr. Fitzgerald, would you comment on these roentgenograms.

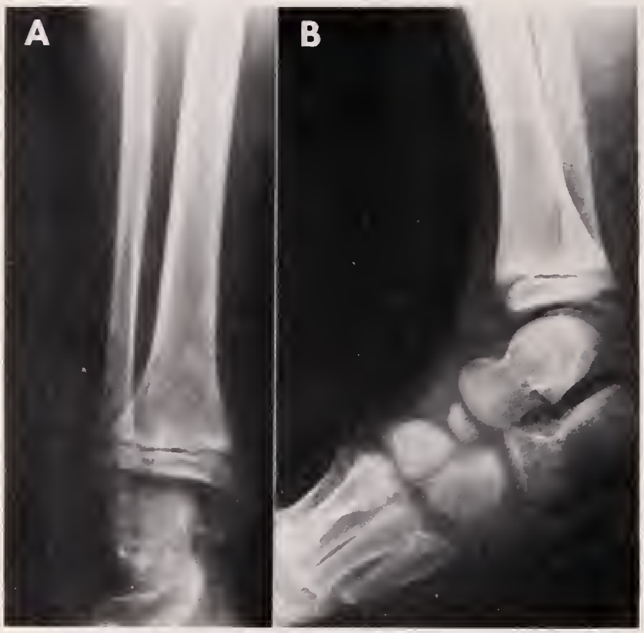

Fig. 3 (Case 2). Right foot after snowmobile injury. (A) Anteroposterior view. (B) Lateral view.

Dr. Edward M. Fitzgerald: They reveal partial loss of his right calcaneus, talus, and distal portion of the fibula.

Dr. Peterson: Note also the soft tissue loss from the heel and the air in the ankle and subtalar joints.

Dr. Fitzgibbons:

The patient was taken to the operating room immediately. Both his peroneal tendons and his abductor digiti quinti had been transected. Also, his distal fibular physis was exposed (Figure 4). Five general anesthetics were required before the wound could be closed, and he was in the hospital for 12 days. He is currently recovering from his injuries.

Case 3

Dr. Fitzgibbons:

The next patient is a 14-year-old boy who was driving a snowmobile while being followed by another boy on a snowmobile, both traveling at an estimated 40 miles per hour. When the second boy attempted to turn abruptly, the ski of his snowmobile struck the patient's lateral left ankle, producing immediate pain and swelling. The next day, he was taken to the emergency room by his mother, and the following roentgenograms were made (Figure 5).

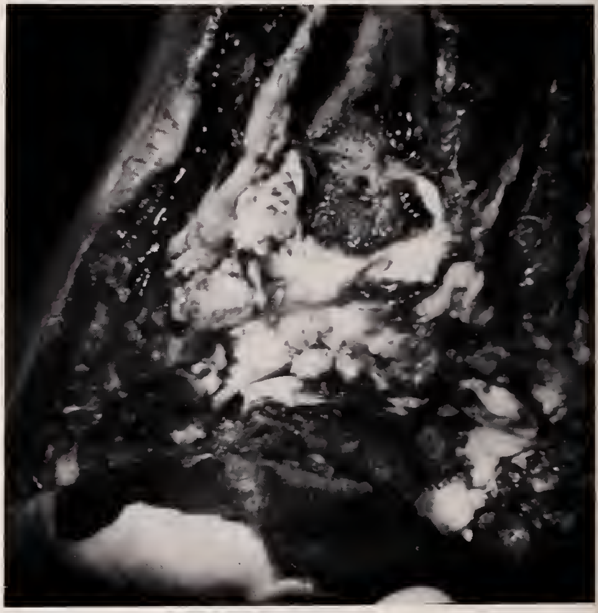

Fig. 4 (Case 2). Lateral side of right foot at time of debridement. Note severe soft tissue loss and exposure of calcaneal, talar, and fibular articular cartilage as well as fibular epiphyseal growth plate.

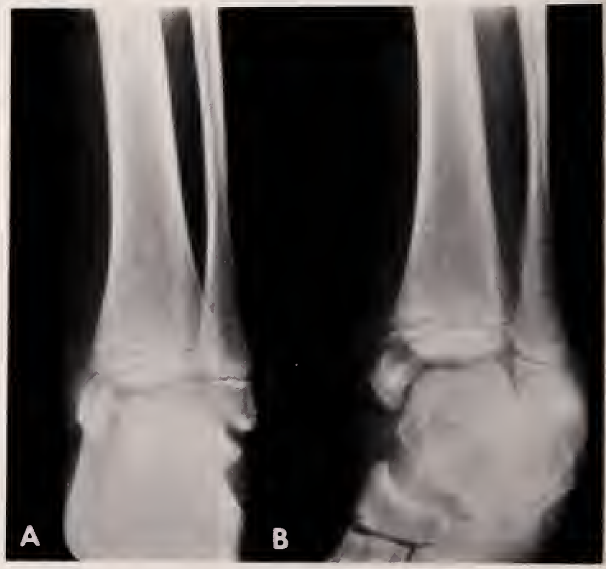

Fig. 5 (Case 3). Left ankle after snowmobile injury. (A) Anteroposterior view. (B) Oblique view.

Dr. Peterson: Dr. Landon, would you comment on these.

Dr. Glenn C. Landon: There is a fracture of the medial malleolus, with some question of involvement of the physis.

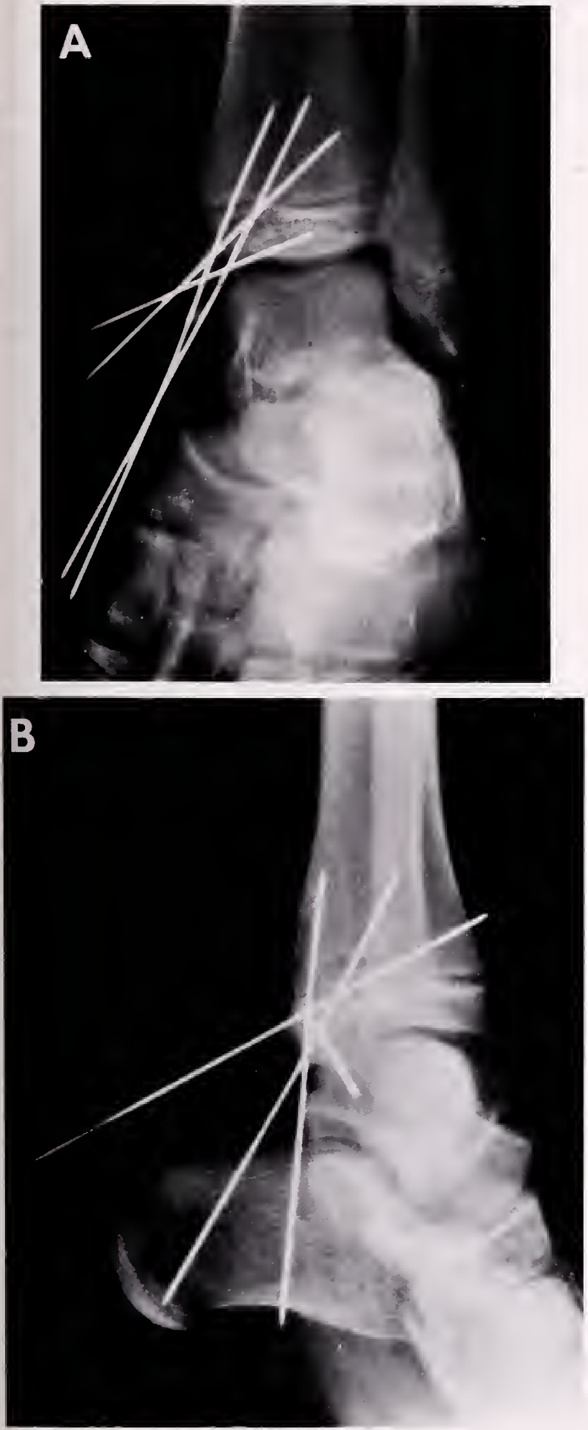

Fig. 6 (Case 3). Ankle at time of open reduction and internal fixation. (A) Anteroposterior view. (B) Lateral view.

Dr. Peterson: How would you treat this injury?

Dr. Landon: I believe open reduction and internal fixation are indicated.

Dr. Fitzgibbons: This patient was taken to the operating room. The physis was found not to be involved, and open reduction and internal fixation were performed (Figure 6).

Dr. Michael A. Arata:

During the past 15 years, snowmobiling has become a popular winter sport in the snow-covered regions of North America. The first snowmobile was built in 1923 by Joseph Armand Bombardier, who mounted a four-cylinder Ford Model T engine on a set of sleigh runners.[1] The design has changed greatly over the years, the present machines weighing between 250 and 400 lb and capable of speeds in excess of 100 miles per hour. By April 1977, more than 316,000 snowmobiles were registered in the state of Minnesota.[2] As the number of snowmobiles in use has increased, so have the injuries related to them. More than 150 deaths occur annually in the United States from snowmobile accidents.[3] In addition, more than 19,000 snowmobile-related injuries are treated in hospital emergency rooms yearly. About 20% of these injuries are in children 16 years of age or younger. Most accidents are the result of traveling at a speed inappropriate for the existing conditions. Mechanical failure resulting in injury tends to occur infrequently. Letts and Cleary,[1] in their four-and-one-half-year retrospective study of snowmobile injuries in children, found that most of the children were from 13 to 16 years old. They also found that most injuries were severe and required lengthy treatment, with the patient staying an average of 22 days in the hospital. The injured child was the driver of the vehicle in 22 instances. Skeletal and soft tissue trauma of the lower extremity occurred with the greatest frequency. Only four epiphyseal injuries were noted in their series. The authors concluded that the child operator of a snowmobile appeared to be particularly vulnerable to

TABLE
Mechanisms of Snowmobile Injury

1. **Snowmobile tipped over**
2. **Snowmobile hit tree**
3. **Snowmobile was hit by a car**
4. **Snowmobile was hit by another snowmobile**
5. **Snowmobile ran off a cliff**
6. **Snowmobile ski struck patient's leg**
7. **Snowmobile moving parts caught patient's clothing**
8. **Snowmobile was driven through a fence**
9. **Snowmobile broke through ice**
10. **Snowmobile handle hit patient's face**

injury and that, similar to results of other studies, the inexperience of the driver tended to increase his chances of injury.

Dr. Fitzgibbons:

Experience at the Mayo Clinic with snowmobile injuries in children agrees with that of Letts and Cleary,[1] because injuries in children have tended to be severe and to require lengthy treatment. From 1971 to 1976, four deaths from snowmobile-related injuries in children were noted at this clinic. We have compiled a list of the mechanisms of injury (Table). Our experience has been that obstacles covered by snow continue to be a major cause of accidents. Recently, however, we have noted injuries suffered when the patient becomes entangled or involved with moving parts of the vehicle, such as the snowmobile track.

A child between ages 12 and 18 is required by law to carry a permit when driving a snowmobile on state land or highways.[4] This permit is obtained by taking a well-organized and well-publicized course in driver education and safety. However, the Department of Natural Resources informs us that these courses are poorly attended. The state has no control over the operation of these vehicles by children on private property, and we have noted that this is where most accidents occur. Snowmobile injuries in children appear to be due to lack of experience with or respect for the vehicle, and control of the use of the vehicle tends to be in the hands of the parents, who usually are the owners of the snowmobile. We must, therefore, encourage the parents of the children who are riding snowmobiles to be sure their children are well informed in the operation and dangers of these vehicles. All potential snowmobile drivers should be encouraged to take the driver and safety education courses available.

References

1. Letts RM, Cleary J. The child and the snowmobile. Can Med Assoc J 113:1061, 1975.
2. International Snowmobile Industry Agency, Washington DC: Personal communication.
3. Accident Facts: Chicago, National Safety Council. p 77, 1974.
4. Minnesota Department of Natural Resources: Personal communication.

MMA Annual Meeting

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Dr. Richard Frey receives Shotwell Award

Dr. Richard J. Frey is the 1978 recipient of the Shotwell Award for noteworthy efforts in the health care field. The award is presented annually by Metropolitan Medical Center.

Among his professional achievements, Dr. Frey has been actively involved in a number of state and local medical organizations. Currently he is chairman of the board of trustees of the Minnesota Medical Association and chairman of the Minnesota Health Care Cost Commission.

The Shotwell Award was established in 1971 in honor of the late Mr. and Mrs. James D. Shotwell in recognition of their significant contributions to Metropolitan Medical Center. The Award is a recreation of the Paul Granlund sculpture "Sprites" that stands in the hospital's courtyard as a symbol of health and well-being.

Review

Experience with Colonoscopic Polypectomy

Review of 700 Polyps

SANTHAT NIVATVONGS, M.D.* and STANLEY M. GOLDBERG, M.D.*

Colonoscopic polypectomy has become the procedure of choice to remove polyps of the entire colon and has largely replaced the traditional colotomy and polypectomy, or colonic resection. The procedure can be safely performed on an outpatient basis in the majority of patients.

THE LOW COMPLICATIONS of colonoscopic polypectomy[6] have made it the procedure of choice to remove polyps of the entire colon.[8] In this review of our own experience with 700 polyps we recommend some guidelines for the various circumstances of colonic polyps.

Material and Methods

From August 1972 to June 1977 700 polyps were removed via the colonoscope from 555 patients at the University of Minnesota Hospitals. All of the patients had previous barium enema studies. Although most examinations revealed either definite or suspicious colonic polyps, a number of the study results were negative. These patients underwent fiberoptic colonoscopy because of persistent bleeding or positive occult blood in the stool.

TABLE 1

Bowel Preparation

3-Day Prep	**Day 3**	**Citrate of magnesia 10 oz** **Low residue diet**
	Day 2	**Citrate of magnesia 10 oz** **Low residue diet**
	Day 1	**Dulcolax, 3 tablets** **Clear liquid diet**
	Day 0	**1 Dulcolax suppository, 2 hours before the procedure**
2-Day Prep	**Day 2**	**Citrate of magnesia 10 oz** **Low residue diet**
	Day 1	**Dulcolax, 3 tablets** **Clear liquid diet**
	Day 0	**1 Dulcolax suppository, 2 hours before the procedure**
1-Day Prep	**Day 1**	**Clear liquid diet** **Citrate of magnesia-8:00 p.m.** **Dulcolax, 3 tablets-10:00 p.m.** **Tap water enemas 1000 ml-8:00 and 9:00 p.m.**
	Day 0	**1 Dulcolax suppository, 2 hours before the procedure**

Prior to polypectomy all of the patients had from one to three days of bowel cleansing, depending upon the time available (Table 1). Bowel cleansing consisted of a low residue diet, citrate of magnesia, Dulcolax tablets, and a clear liquid diet on the day before colonoscopy. Tap water enema was given only with the one-day cleansing preparation, the evening before the procedure. Each patient also received a Dulcolax suppository two hours before colonoscopy. Immediately prior to the procedure each patient received 5-10 mg of Diazepam, intravenously; a supplement of 50 mg Meperidine was required during the procedure in only few patients. Oral antibiotics were used in the first 200 polypectomies.

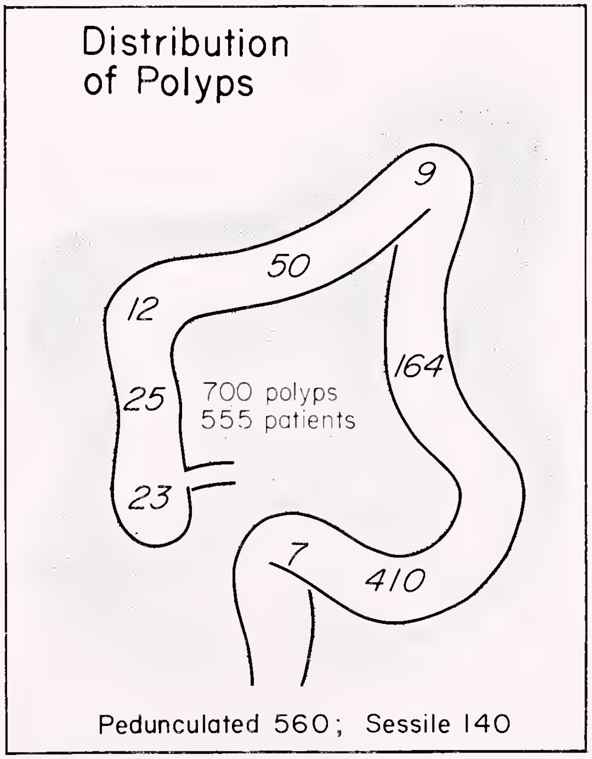

Fig. 1 — Distribution of polyps.

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*Division of Colon & Rectal Surgery Department of Surgery, University of Minnesota, Minneapolis.

See editorial page 171.

Since January of 1975 colonoscopic polypectomies have been performed on an outpatient basis unless the patients were already in the hospital. The outpatients were discharged shortly after the procedure whereas the inpatients usually stayed overnight. All patients continued on a low residue diet for one week and were instructed to report any instances of fever, persistent abdominal pain, or profuse rectal bleeding. We used an Olympus CFMB 110 cm colonoscope to remove the first 200 polyps and either a CFLB or CFLB2 185 cm scope to remove the remainder.

Results

Distribution and Size of Polyps (Figure 1)

Of the 700 excised polyps, 560 were pedunculated and 140 were sessile. Eighty-three per cent of the polyps were located in the left colon, 10 per cent in the transverse colon and 7 per cent in the right colon. The size of the polyps ranged from 5 mm to 5 cm; 60 per cent were between 1-2 cm (Figure 2).

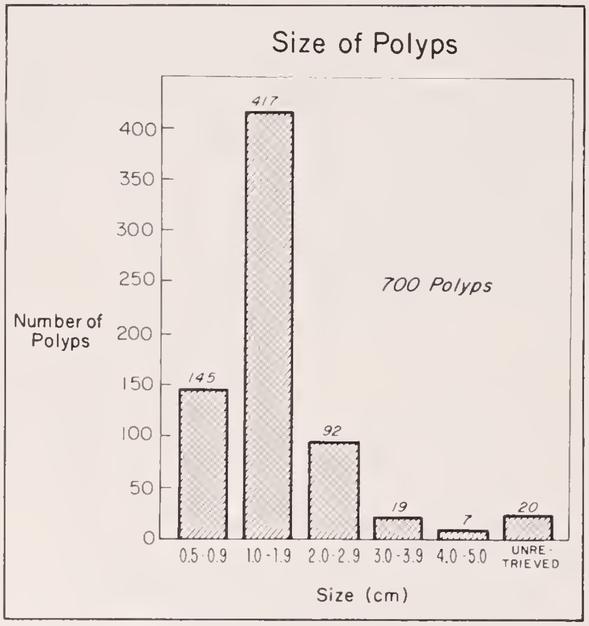

Fig. 2 — Size of polyps.

Pathology (Table 2)

Seventy-eight per cent of the polyps were adenomatous, villoglandular or villous types. Twenty-two polyps, 3 per cent, contained superficial carcinoma and 25 polyps, 4 per cent, had invasive carcinoma.

Number of Polyps in each Patient (Table 3)

Seventy-eight per cent of our patients had only one polyp. The largest number of polyps removed from one patient was 17.

TABLE 2

Pathology

Benign adenomatous or villoglandular polyp	537
Villous adenoma	12
Polyp with superficial Ca	22
Polyp with invasive Ca	25
Juvenile polyp	22
Hamartoma (Peutz-Jeghers Syndrome)	2
Hyperplastic polyp	28
Lipoma	6
Lymphosarcoma	1
Miscellaneous	25
Unretrieved	20
	700

TABLE 3

Number of Polyps in Each Patient

No. of Polyps	No. of Patients
1	439
2	83
3	22
4	2
5	5
more than 5	4
	555

Complications

Five of our 555 patients experienced complications after polypectomy. Three patients lost from 350-400 ml of blood, but did not require a blood transfusion. One patient developed fever and air was noted around the wall of the ascending colon, and another patient had fever and peritoneal signs. Both patients were treated successfully with antibiotics and required no operative intervention. No free perforation occurred as a result of polypectomy. All the complications took place in the first 150 polyps removed.

Discussion

Bowel Preparation

It is essential that the colon is clean before colonoscopy, therefore we prefer to extend the bowel preparation, with laxative, to three days. If time is limited, however, a vigorous overnight preparation is also satisfactory (Table 1). We do not give the patients an enema on the day of the procedure because we found the colon to be drier and more satisfactory without it. Carbon Dioxide is not used for polypectomy. Bond and Levitt[1] have shown that the danger of explosion in a well-prepared colon is negligible. We no longer use antibiotics because of the low complications from the procedure.

Inpatient or Outpatient

With more skill, we have become confident in erforming the procedure as an outpatient. During the ast 2.5 years, unless the patients were already in the ospital, we performed most of the polypectomies on n outpatient basis. A small number of patients — the lderly, those with severe systemic disorders, and hose in whom a clean colon was not achieved — were dmitted one day before the procedure. Most patients rom out-of-town were requested to stay in the city vernight. We have not had any complications for the ast 550 polypectomies.

Retrieval of Polyp

The most practical and satisfactory method of polyp etrieval was the suction at the tip of the colonoscope. Occasionally we used tap water or saline enemas to wash out the polyps. We found the polyp grasper to be clumsy and impractical. Twenty of the excised polyps, 3 per cent, were lost.

Polyps not reached by Colonoscope

In a small number of patients the areas indicated on heir barium enema studies could not be reached by colonoscope. The most common causes were fixation of the sigmoid colon from a previous pelvic operation, and severe diverticular disease. These cases should be examined again, using a barium enema study, preferably with an air contrast to confirm the original indings. If the presence of a polyp is confirmed, and ts size is 1 cm or larger, operative removal should be considered: 13 of the 25 polyps with invasive carcinoma from our series were between 1-1.5 cm in ize.

Carcinoma missed by Colonoscopy

In three instances carcinoma of the right colon was undetected by total colonoscopy, although it was ubsequently detected. It is our policy to repeat the colonoscopy, barium enema study, or even to perform a laparotomy if the history and clinical findings suggest he presence of colonic carcinoma.

Patients with Rectal and Colonic Carcinoma

There is still no general agreement whether one should perform a colonoscopy in patients with carcinoma of the colon or rectum who have had adequate barium enema study results. Objections for colonoscopy in these cases are the danger of perforating the carcinoma, especially in the left colon, and the theoretical spreading of cancer cells by the procedure. Our practice is to do colonoscopy in patients with carcinoma of the right or transverse colon, because an additional finding of polyp or carcinoma may change the extent of the colonic resection. We avoid doing colonoscopy in patients with rectal or left colonic carcinoma complicated by narrowing of the lumen.

Patients with Benign Colonic Polyps

The risk of developing a secondary polyp, or carcinoma, is higher in patients who have undergone polypectomy.[3,5] These patients should have a total colonoscopy at least once, if possible, then colonoscopy or barium enema with air contrast every three years.

Selection of Polyps to be Excised via Colonoscope

Colonoscopic polypectomy is potentially dangerous, and the patients must be selected carefully. Visualizing the gross appearance of the lesion through the scope, the colonoscopist must decide immediately whether to biopsy, fulgurate, excise or leave the tissue alone. Almost all of the pedunculated polyps of any size can be safely removed in one piece via the colonoscope. Many sessile polyps are removed piecemeal, occasionally in more than one session. All flat polyps with the bases larger than 2 cm should be reserved for colon resection. Sessile polyps with induration and ulceration are signs of invasive carcinoma. Colonoscopy has no place in the treatment of a frank carcinoma.

Polyp with Superficial Carcinoma

Colonic polyps with superficial carcinoma or carcinoma in-situ never metastasize,[2,7] therefore complete excision is an adequate treatment. The followup of these patients is the same as for patients with benign polyps.

Polyp with Invasive Carcinoma

Problems often arise on what to do when the polyp removed via colonoscope is later found to be an invasive carcinoma. We have 25 such polyps (4 per cent). It is essential to study the histologic detail of these polyps to determine appropriate treatment.[4] In general, all sessile polyps with invasive carcinoma, or pedunculated polyps with carcinoma invading into the stalks, require colon resection. Pedunculated polyps with invasive carcinoma limited to the head require no further treatment. We followed these patients with CEA and a colonoscopy at two, six, and 12 months, thereafter, colonoscopy alternated with barium enema every other year.

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Minnesota Medical Association

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- * Upper Respiratory Infection: Common ENT Problems in Childhood
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Minnesota Medical Association

Syllabus

A compendium or summary outline of a discourse, treatise, course of study or examination requirements; a series of abstracts.
(Webster)

Asphyxia and Resuscitation

RODERICK KRUEGER, M.D.*

In recent years' modern technology, skilled medical care has allowed for the survival of smaller and smaller infants. There is, however, a segment of the intensive care unit's population which continually frustrates the staff since before they begin the fight the battle is frequently lost. This is the area of perinatal asphyxia. Every hour a new infant will be stricken with cerebral palsy and 90% of these are secondary to perinatal asphyxia. It has been estimated that 20% of newborns experience oxygen deprivation which might affect subsequent neurologic development. Some perinatal asphyxia can be prevented by identification of the high risk obstetrical patient. Fetal heart rate monitoring can further detect distress during labor and alerts the physician to perinatal asphyxia. One must be prepared to identify, immediately resuscitate, and stabilize any infant with asphyxia. Only with aggressive and early treatment can the prognosis of these infants be improved. The following is an outline reviewing the pathophysiology of asphyxia on the brain, its clinical presentation, and an approach to resuscitation of the asphyxiated infant and one's immediate management of it.

II Pathophysiologic Effects on the Brain

- A. Preterm — damage is periventricular with sparing of the cortical mantle and commonly leads to intraventricular bleeds.
- B. Term — damage is peripherally in the cerebral cortex and underlying white matter. Intraventricular bleed is less common.
- C. Possible Steps Involved: Asphyxia → redistribution of blood flow to organs → oxygen debt to brain cells → intracellular swelling → focal ischemia → general brain swelling → increased intra-cranial pressure → cerebral necrosis → atrophic cortical necrosis.

III Clinical Features

- A. First 12 hours
  - 1—Loss of tone (first to go and last to return frequently).
  - 2—State of consciousness altered — frequently obtunded or stuporous.
  - 3—Seizures — usually after two hours of age amd may be subtle, i.e. tonic deviation of the eyes, lip smacking, apnea, tonic seizures, multifocal clonic seizures.
- B. 12 to 24 Hours
  - 1—Level of consciousness may improve
  - 2—Seizures increase in frequency and severity
  - 3—Infants may become jittery (i.e. hypocalcemia, hypoglycemia)
  - 4—Weakness — upper extremities in term infants and lower extremities in preterm infants.
- C. 24 to 72 Hours
  - 1—Level of consciousness again deteriorates.
  - 2—Brain stem involvement — skew deviation of eyes, respiratory arrest, fixed pupils, loss of doll's eyes.
  - 3—If preterm — intraventricular bleed
- D. 72 Hours and Beyond
  - 1—Slow improvement
  - 2—Feeding problems secondary to cranial nerve deficit
  - 3—Residual damage

IV Asphyxia can be defined as having an Apgar score of less than five at one and five minutes with or without shock. It has been pointed out by Tooley in San Francisco that a significant number of infants with one and five minute apgars greater than five have serum pH levels less than 7.10.

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*Duluth, Minnesota.

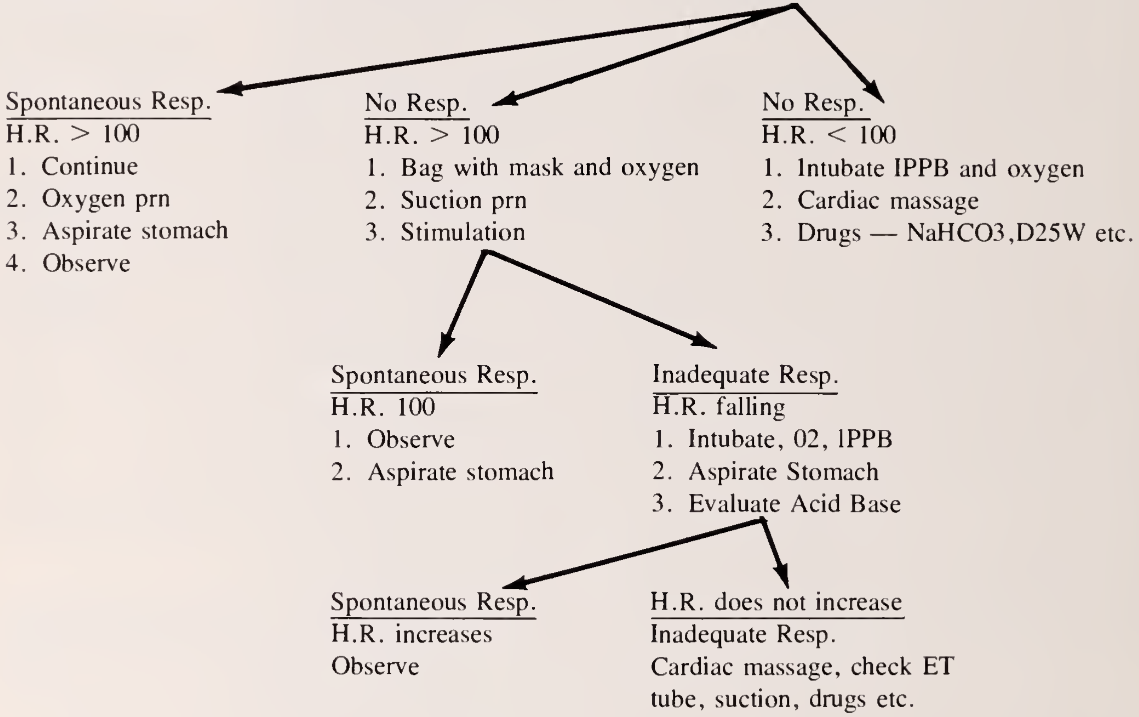
Apgar ratings can be used to determine steps needed for adequate resuscitation, but one can also do it in terms of "primary" and "secondary" apnea. "Primary" apnea is the initial period of apnea following asphyxia during which time a variety of stimuli will initiate gasping. "Secondary" apnea, also referred to as terminal apnea, may follow. Stimuli will not initiate gasping and vigorous cardiopulmonary resuscitation is needed. Heart rate can be an indicator as to whether an infant is having "primary" or "secondary" apnea. If the heart rate is over 100/min. the infant is probably in "primary" apnea and stimuli and oxygen may be all that is necessary to initiate respiratory activity. The following is an approach to identifying "primary" or "secondary" apnea, based on an initial evaluation of heart rate and respiratory activity. A course of action is then proposed.

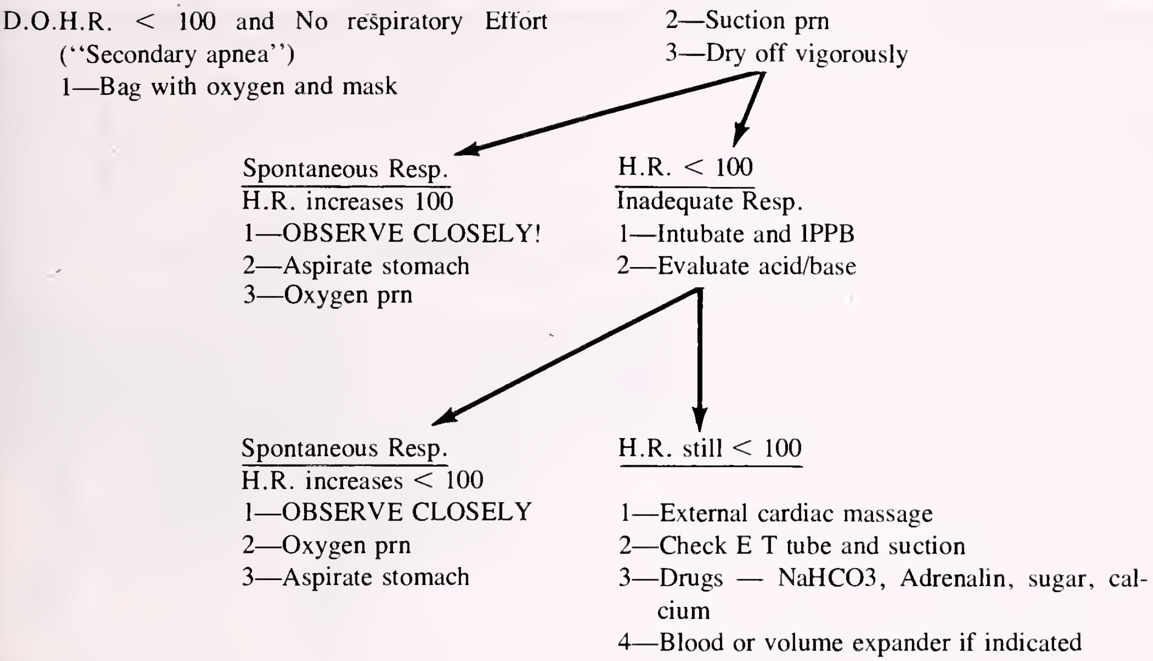
V Steps for Resuscitation

A. Steps done in all cases
  1—Place in head down position
  2—Suction mouth and then nose
  3—Listen to heart rate and for respiratory activity

B. H.R. > 100 and Good Respiratory Activity
  1—Dry off with towels
  2—Oxygen by tubing prn for color
  3—Aspirate the stomach
  4—Observe

C. H.R. > 100 And No Respiratory Effort ("Primary" apnea)
  1—Oxygen to fact with tubing
  2—Dry off vigorously


Spontaneous Resp.
H.R. > 100
1. Continue
2. Oxygen prn
3. Aspirate stomach
4. Observe
No Resp.
H.R. > 100
1. Bag with mask and oxygen
2. Suction prn
3. Stimulation
No Resp.
H.R. < 100
1. Intubate IPPB and oxygen
2. Cardiac massage
3. Drugs — NaHCO3,D25W etc.
Spontaneous Resp.
H.R. 100
1. Observe
2. Aspirate stomach
Inadequate Resp.
H.R. falling
1. Intubate, 02, IPPB
2. Aspirate Stomach
3. Evaluate Acid Base
Spontaneous Resp.
H.R. increases
Observe
H.R. does not increase
Inadequate Resp.
Cardiac massage, check ET tube, suction, drugs etc.



D.O.H.R. < 100 and No respiratory Effort
("Secondary apnea")
1—Bag with oxygen and mask

2—Suction prn
3—Dry off vigorously

Spontaneous Resp.
H.R. increases 100
1—OBSERVE CLOSELY!
2—Aspirate stomach
3—Oxygen prn

H.R. < 100
Inadequate Resp.
1—Intubate and IPPB
2—Evaluate acid/base

Spontaneous Resp.
H.R. increases < 100
1—OBSERVE CLOSELY
2—Oxygen prn
3—Aspirate stomach

H.R. still < 100

1—External cardiac massage
2—Check E T tube and suction
3—Drugs — NaHCO3, Adrenalin, sugar, calcium
4—Blood or volume expander if indicated

Volume expansion in the absence of volume depletion could cause pulmonary edema. Over ventilation may alter blood flow to the brain, cause respiratory alkalosis and if associated with hypoglycemia or hypocalcemia could precipitate seizure activity. Drugs should not be considered until adequate ventilation and perfusion have been provided. This can correct up to 50% of any base deficit suffered secondary to asphyxia.

VI Drugs Used

A. NaHCO3 1-4 meq/kg diluted 1:1 with sterile water and given over 5-10 minutes slow IV. Be conservative.

B. Volume Expanders
  1—Salt poor albumin — 1 gm/kg diluted to a 5% solution with lactated ringor solution.
  2—Whole Blood — 10-20 ml/kg (0 Rh neg low titer or 0 Rh neg packed cells resuspended in AB plasma.
  3—Plasmanate — 10-20 ml/kg.

C. Calcium gluconate 10% — 2ml/kg IV over ten minutes watching for bradycardia.

D. D25W 2-4 ml/kg IV slow push followed with a continuous IV of D10W.

E. Epinephrine 1:10,000 — 0.1-0.5 ml IV, intracardiac, or through the endotracheal tube followed by IPPB.

VII Infants who present with no spontaneous respiratory activity and low heart rate may be suffering from maternal drug depression and this needs to be distinguished from perinatal asphyxia.

MATERNAL DRUG DEPRESSION
1—Positive history
2—No meconium before birth
3—Skin cyanotic
4—Slow H.R. but strong pulse
5—Fair tone
6—Responds quickly to ventilation

PERINATAL ASPHYXIA
1—Negative History
2—Meconium often passed before birth
3—Skin pale
4—Slow H.R. and weak pulse
5—Hypotonic
7—Often requires vigorous resuscitation.

The treatment for maternal drug drpesssion is Naloxone (Narcan) 0.01 mg/kg IM. Be sure you use the pediatric vial. This will usually come out to ½ vial in the premature and a full vial in the infant who is term.

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VIII Treatment of Asphyxia After Immediate Resuscitation Efforts

A. Asphyxia has an effect on all organs and the decreased perfusion, as well as increased capillary permeability leads to the following possibilities: hepatic necrosis, pulmonary edema, necrotizing entercolitis, renal vein thrombosis, decreased cardiac output, cardiac dilatation etc. Treatment must therefore take into consideration all of these organ systems. If the patient is digitalized because of cardiac failure and he also has acute renal failure he may easily become toxic. Over use of volume expanders may cause pulmonary edema.

B. Basic Concepts

1—Maintain close intake and output with frequent weights

2—Keep fluids low (insensible water loss plus renal output)

3—Observe for signs of IADH (low serum osmolarity, increased sodium excretion in the urine) RESTRICT FLUIDS.

4—Check Dextrostix frequently and prevent hypoglycemia. Some people feel the serum flucose should be around 120-200 mg% to maintain adequate glucose concentrations in the brain.

5—Treat seizure activity. Phenobarbital 10 mg/kg slow IV loading dose followed by a maintenance dose of 5-10 mg/kg/day. Dilantin can also be used in the same dosages if necessary. Avoid Valium since if used with phenobarbital could potentiate cardiac arrest and it is too short acting.

6—Begin feeds after the infant is stable and go slowly watching for signs of necrotizing enterocolitis.

7—Manitol and Lasix have been tried by some but could potentiate intracranial bleeds by rapid intracellular depletion of fluid in the brain. These need further studies.

Continuing Medical Education

Minnesota Society of Clinical Pathologists

Spring Meeting: Saturday, April 21, 1979

Symposium on Hematopathology:

1. "Serum Ferritin — Use and Interpretation in the Diagnosis of Iron-Deficiency States" by Dr. Virgil Fairbanks, Mayo Clinic.
2. "Monitoring Heparin Therapy in DIC and Other Diseases" by Dr. Francis Kazmier, Mayo Clinic.
3. "Membrane Surface Markers in Lymphocytic Leukemias" by Dr. Richard Brunning, University of Minnesota.
4. "Pre-Leukemia" by Dr. Robert Pierre, Mayo Clinic.
5. "Recent Advances in the Diagnosis of Malignant Lymphoma" by Dr. Glauco Frizzera, University of Minnesota.

University of Minnesota — Health Sciences Building A, Room 2690. Approved for CME #I Credits, 5 Hours. Contact: Dr. Charles Horwitz, Mt. Sinai Hospital, Minneapolis.

Mayo Clinic

The Department of Pediatrics of the Mayo Clinic is sponsoring Pediatric Days, April 27-28, 1979, in Rochester, Minnesota. The program theme is "Health Problems in the Adolescent" and faculty will consist of Mayo Clinic Pediatric Staff and specialists from other departments. The Amberg-Helmholz Lecture will be given by Dr. Michael I. Cohen, Department of Adolescent Medicine, Albert Einstein School of Medicine.

Inquiries can be directed to the Program Director, Robert H. Feldt, M.D., Professor of Pediatrics, Mayo Medical School, Rochester, Minnesota 55901.

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12 PHYSICIAN, multi-specialty clinic needs an Ob-Gyn. Ours recently retired. The present group includes general surgeons, internists, a urologist, an ophthalmologist, an otolaryngologist and family practitioners. Northeastern Minnesota location with complete hospital facilities. Excellent recreation country, both summer and winter. Solid and growing economic conditions. No big city problems. Please call collect relative to any questions. Reply — Mesaba Clinic, Hibbing, MN 55746 or call John Brust at (218) 262-3441.

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(Continued on Page 209)

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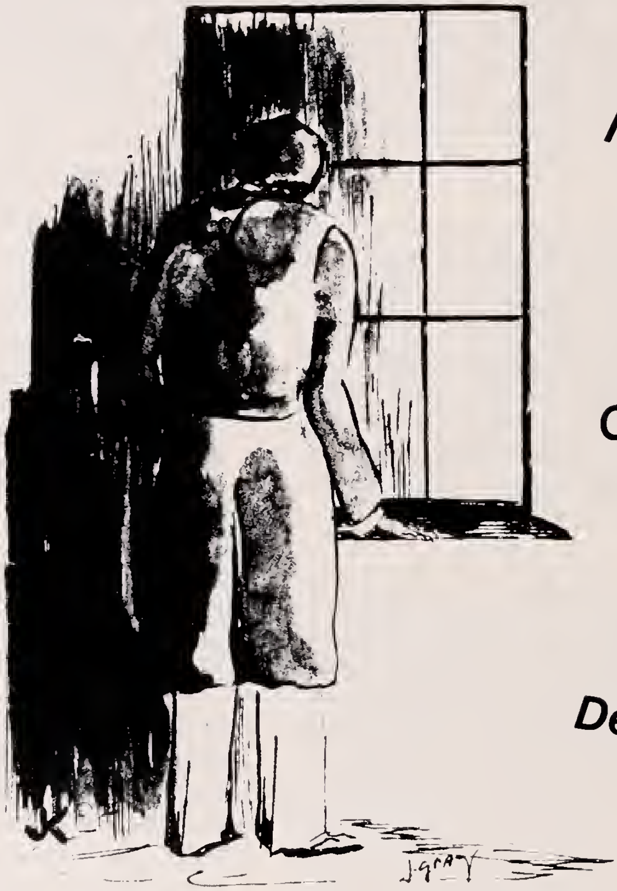
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(Continued from page 207)

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WANTED: Orthopedic surgeon, Board Certified or eligible to join nine man group consisting of 8 family practitioners and general surgeon in University town with trade area population of 22,000, 30 miles southeast of St. Paul, MN JCAH approved hospital. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, Ltd., River Falls, WI 54022, or call collect (715) 425-6701.

FAMILY PRACTITIONERS needed immediately to join present three physician corporate group practice in rural Southwestern Minnesota; guaranteed income with liberal fringe benefits; full partnership after one year; no investment necessary; new clinic facility attached to newly renovated hospital; area offers excellent recreational activities; top school systems; warm community atmosphere. Contact J. L. Bader, M.D., Chief of Staff, Slayton Clinic, 2744 Broadway Avenue, Slayton, MN 56172; Phone number: (507) 836-6153 or 836-6463.

(Continued to Page 210)

(Continued from Page 209)

TWENTY-TWO MAN multi-specialty clinic in Minneapolis area desires additional OB-GYN doctor for expanding OB-GYN practice. Excellent salary and fringe benefits. Must be board certified or board eligible. Contact Mr. T. Signorelli, 3620 Central Avenue N.E., Minneapolis, MN 55418.

GENERAL SURGEON or internist needed to take over 27 year practice by May-July, 1980, in two college city. 42 miles from Twin Cities. Write: MINNESOTA MEDICINE — 543 — 101 E. 5th St. #900, St. Paul 55101.

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Minnesota Physiatric Society

The Minnesota Physiatric Society wishes to call the attention of Minnesota physicians to Chapter 55 of the Minnesota Uniform Building Code, which requires that new apartments and public buildings be accessible to physically handicapped persons.

Without accessibility in newly constructed apartments and public buildings, persons with advancing age, arthritis, myocardial infarctions or hemiplegia, and also younger persons with spinal cord and cerebral injuries, are severely and unjustly limited in their ability to participate in today's life. We all wish to continue to live without physical barriers in our environment as we advance in age.

Chapter 55 of the Uniform Building Code is being circumvented by builders in our state. The physiatrists of Minnesota endorse unanimously the resolution of the Committee on Rehabilitation and the House of Delegations of MMA in their resolution to support strongly the enforcement of the concept of a barrier-free environment in public and commercial buildings, housing, and transportation in our state.

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MMA Annual Luncheon
May 17, 1979
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"Why Don't They Tell The Truth About Old Age?", George Sheehan, M.D., Redbank, New Jersey — cardiologist, Best-selling author, columnist, marathon runner.

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For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

ach tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

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- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
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- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension*, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

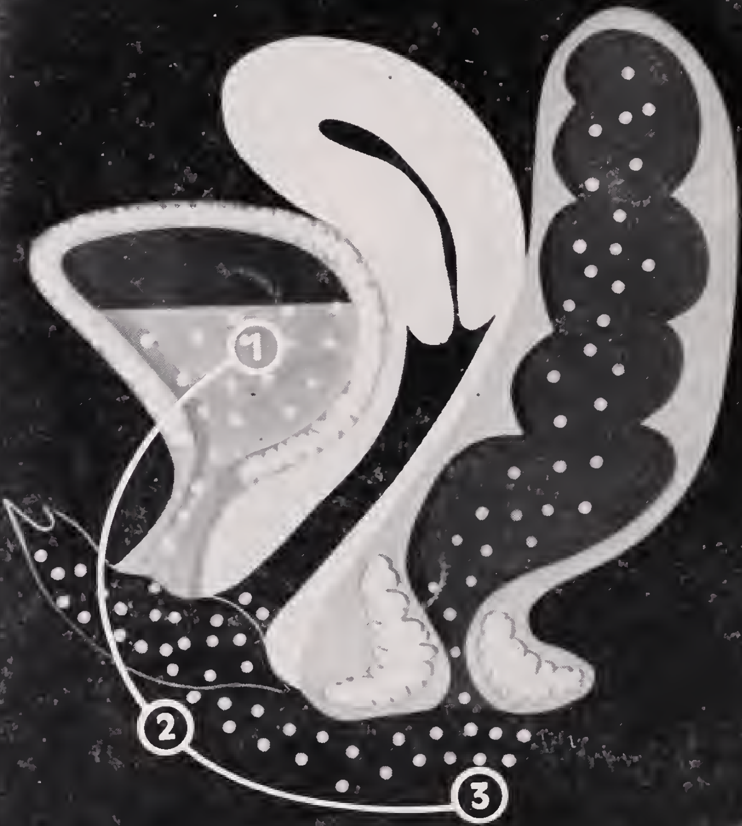
ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see back cover.

Her next attack of cystitis may require

the Bactrim™ 3-system counterattack



Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Ente bacteriaceae* in the bowel without the emergence of r sistant organisms. Thus, Bactrim reduces the risk of intr colonization by fecal uropathogens. It has *no* significant effect on other normal, necessary intestinal flor

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal tract

Please see reverse side for summary of product information.

minnesota medicine

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April 1979

PEDIATRIC INDICATIONS* FOR BACTRIM CONTINUE TO GROW...

URINARY TRACT INFECTIONS

PNEUMOCYSTIS CARINII PNEUMONITIS

SHIGELLOSIS

ACUTE OTITIS MEDIA

*Involving susceptible organisms.

Please see Indications section in summary of product information on last page of this advertisement.

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100 ml
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for 10 days
Repeat
Dr. H. Quinn
Be sure to specify

*Pr cription
or 10-kg
2 b] child)*

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s'Bactrim Suspension." The same active ingredient formulation—the difference is the flavor.*

raindicated in children under 2 months of age.

Please see summary of product information on following page.

BACTRIM ROCHE
(trimethoprim and sulfamethoxazole)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note* The increasing frequency of resistant organisms limits the usefulness of all antibacterials especially in these urinary tract infections
For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. Limited clinical information presently available on effectiveness of treatment of otitis media with Bactrim when infection is due to ampicillin-resistant *Haemophilus influenzae*. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.
For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.
Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.
Contraindications: Hypersensitivity to trimethoprim or sulfonamides pregnancy nursing mothers infants less than two months of age
Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin Deaths from hypersensitivity reactions, agranulocytosis aplastic anemia and other blood dyscrasias have been associated with sulfonamides Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides Sore throat fever pallor purpura or jaundice may be early signs of serious blood disorders Frequent CBC s are recommended therapy should be discontinued if a significantly reduced count of any formed blood element is noted
Precautions: Use cautiously in patients with impaired renal or hepatic function possible folate deficiency, severe allergy or bronchial asthma In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur During therapy maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination and renal function tests, particularly where there is impaired renal function Bactrim may prolong prothrombin time in those receiving warfarin reassess coagulation time when administering Bactrim to these patients
Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim *Blood dyscrasias* Agranulocytosis, aplastic anemia megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia *Allergic reactions* Erythema multiforme, Stevens-Johnson syndrome generalized skin eruptions, epidermal necrolysis, urticaria serum sickness, pruritus exfoliative dermatitis, anaphylactoid reactions, periorbital edema conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis *Gastrointestinal reactions* Glossitis, stomatitis, nausea emesis, abdominal pains, hepatitis, diarrhea and pancreatitis *CNS reactions* Headache peripheral neuritis, mental depression, convulsions ataxia, hallucinations, tinnitus, vertigo, insomnia apathy, fatigue, muscle weakness and nervousness *Miscellaneous reactions* Drug fever chills, toxic nephrosis with oliguria and anuria periarteritis nodosa and L E phenomenon Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production diuresis and hypoglycemia in patients, cross-sensitivity with these agents may exist In rats, long-term therapy with sulfonamides has produced thyroid malignancies
Dosage: Not recommended for infants less than two months of age.
URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN AND ACUTE OTITIS MEDIA IN CHILDREN
Adults Usual adult dosage for urinary tract infections—1 DS tablet (double strength) 2 tablets (single strength) or 4 teasp (20 ml) b i d for 10-14 days Use identical daily dosage for 5 days for shigellosis
Children Recommended dosage for children with urinary tract infections or acute otitis media—8 mg kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days Use identical daily dosage for 5 days for shigellosis A guide follows
Children two months of age or older

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
22	10	1 teasp (5 ml)	½ tablet
44	20	2 teasp (10 ml)	1 tablet
66	30	3 teasp (15 ml)	1½ tablets
88	40	4 teasp (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment

Creatinine Clearance (ml min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

PNEUMOCYSTIS CARINII PNEUMONITIS Recommended dosage 20 mg kg trimethoprim and 100 mg kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days See complete product information for suggested children s dosage table
Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100 Tel-E-Dose® packages of 100, Prescription Paks of 20 *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500, Tel-E-Dose® packages of 100, Prescription Paks of 40, available singly and in trays of 10 *Pediatric Suspension*, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole cherry flavored—bottles of 16 oz (1 pint) *Suspension*, containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored bottles of 16 oz (1 pint)

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April 4–7	**Tennessee Medical Association** Airport Milton Inn Memphis, Tennessee
April 19–21	**Alabama Medical Association** Birmingham Hyatt House, Civic Ce Birmingham, Alabama
April 19–22	**Missouri State Medical Associatio** Chase-Park Plaza Hotel St. Louis, Missouri
April 20–22	**Georgia Medical Association** De Soto Hilton Savannah, Georgia
April 21–22	**Iowa Medical Society** Hyatt House Des Moines, Iowa
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April 25–29	**Arizona Medical Association** Safari Hotel Scottsdale, Arizona
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Contents — April, 1979

COVER PHOTOGRAPH — "The Sloop 'Tiercel'"
Alvin Schultz, M.D. ... 265

PRESIDENT'S LETTER — My Special Invitation to You
Robert S. Flom, M.D.
President, Minnesota Medical Association ... 217

EDITOR'S NOTEBOOK — The U.S. Health Care System — The Next Ten Years: Government Regulation, Private Competition, or Something In-between?
Richard L. Reece, M.D.
Editor-in-Chief ... 219

ORIGINAL CONTRIBUTIONS

Cholelithiasis in a Child without Hemolytic Anemia
Michael J. Weiner, M.D. ... 223

Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage
Kenton Bodily, M.D. and Ronald P. Fischer, M.D. ... 225

Micropolycystic Liver Occurring in an Adult with Gluten Enteropathy
C. E. Weigent, M.D. and K. C. Hanson, M.D. ... 231

Acute Viral Myocarditis — Clinical and Histologic Changes
C. M. Bandt, M.D. et al. ... 234

An Adult Phenylketonuric with Schizophrenia — Clinical and Biochemical Similarities and Possible Genetic Connection between the Two Diseases
Robert O. Fisch, M.D. et al. ... 243

Post-Operative Headache — A Manageable Complication
John B. Brainard, M.D. ... 247

EDITORIALS

Mononuclear Infiltrates in the Myocardium
Charles R. Meyer, M.D. ... 253

Cholelithiasis in a Child without Hemolytic Anemia
Stuart Lane Arey, M.D. ... 253

Micropolycystic Liver and Gluten Sensitivity — So What?
C.A. Pierach, M.D. ... 255

Cholestasis of Pregnancy — *William C. Meyer, M.D.* ... 255

Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage — *Joseph C. Kiser, M.D.* ... 257

REPORT OF MMA NOMINATING COMMITTEE ... 218

LETTER TO THE EDITOR — The Barium Enema: Is It Alive?
H. Charles Walker, Jr., M.D. et al. ... 259

RHEUMATOLOGY CORNER — Planning A Treatment Program for the Patient with Rheumatoid Arthritis — *John G. Mayne, M.D.* ... 250

REVIEW — Cholestasis of Pregnancy
Donald S. Mattson, M.D. and Gregory M. Olson, M.D. ... 261

MINNESOTA DEPARTMENT OF HEALTH — Misconceptions about Possibly Rabid Animals that Have Bitten Humans
Michael R. Peterson, D.V.M. and Barry S. Levy, M.D. ... 266

LEGISLATION — Minnesota "Brain Death" Legislation: A Step Forward... Or Backward?
John M. Burns, M.D. and John S. Hamlon, M.A. ... 273

SPECIAL ARTICLE — Metropolitan Medical Office Building Fire — The Event and its Consequences
David Moody, M.D. and Jim Thalhuber ... 279

OBSTETRICS — GYNECOLOGY — Colposcopy Experience at St. Louis Park Medical Center — *Arlyn A. Hamann, M.D.* ... 283

MINNESOTA MEDICAL ASSOCIATION — Annual Meeting Scientific Program
Stuart Thorson, M.D.
Chairman, Scientific Assembly Subcommittee ... 289

CONTINUING MEDICAL EDUCATION ... 227, 233, 237, 246, 249, 265, 268, 289, 308

BOOK REPORTS — *Reuben Berman, M.D., Editor Emeritus* ... 257
Richard L. Reece, M.D., Editor-in-Chief ... 257

CLASSIFIED ADVERTISEMENTS ... 286

INDEX TO ADVERTISERS ... 238

Volume 62:4
Pages 211-308

MINNESOTA MEDICINE REPRESENTS

- Association of Neurologists of Minnesota
- Duluth Surgical Society
- Hennepin County Psychiatric Society
- Minneapolis Academy of Medicine
- Minneapolis Surgical Society
- Minnesota Academy of Family Physicians
- Minnesota Academy of Medicine
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- Minnesota Orthopaedic Society
- Minnesota Physiatric Society
- Minnesota Society of Anesthesiologists
- Minnesota Society of Clinical Pathologists
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- Minnesota Medical Association
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President's Letter

My Special Invitation to You

Included in this issue is the program of events and presentations which are planned for your Annual Meeting in St. Paul this year. Dr. John Burns, Local Arrangements Chairman, has arranged some exciting innovations including an old fashion medicine show and special dinner suggestions at some of St. Paul's excellent restaurants, for renewing old friendships and meeting new friends. I invite you all to my home town, St. Paul, for this galla event in May.

A special guest will be Dr. Hoyt Gardner, President-Elect of the American Medical Association. We hope you will all avail yourselves of the opportunity to meet him and hear him speak.

Incidentally, the Minnesota Medical Association has announced the candidacy of Dr. Robert Kelly of Grand Rapids for the AMA Board of Trustees and would hope that each of you will support his campaign in every way you can.

Come to St. Paul in May to participate in the scientific program, the fun, the deliberations of the House of Delegates. Be aware that every member is welcome and has a right and responsibility to be heard at the Reference Committees on any issue he or she has feelings.

This is your organization, and its vitality depends upon your participation.

Robert S. Flom

Robert S. Flom, M.D.
President
Minnesota Medical Association

REPORT OF THE NOMINATING COMMITTEE

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MINNESOTA MEDICINE 1919

Editor's Notebook

The U.S. Health Care System — The Next Ten Years:

Government Regulation, Private Competition, or Something In-between?

> *"Only one conclusion can safely be ventured: the polemicist who believes he knows what will happen is likely to be wrong. There are simply too many interacting variables to permit even the most skillful analyst to anticipate all future developments. We can, however, consider the principal health-service goals on the nation's agenda and estimate the probabilities of accomplishing them in light of the existing power centers and decision-making mechanisms."*
>
> Eli Ginzberg, Professor of Economics, Columbia University,
> "Health Services, Power Centers, and Decision-Making
> Mechanisms," *Doing Better and Feeling Worse,* 1977

One day last week, during a coffee forum in the hospital medical staff room, these two questions were being batted about: (1) When do you think a National Health Bill will pass? (2) Would you advise your child to become a doctor?

Variable Answers

Answers varied, but went like this for question 1: "The bill will pass in a few years, as soon as the economy gets straightened out." "Kennedy and the press have too much power. We can't hold it off for long." "It's a matter of time. Bureaucrats always win. Thank God, I'm retiring."

And like this for question 2: "No, Medicine won't be fun anymore when my son grows up." "No, once the government gets its hands in things, it will tell future doctors what to do." "I don't think so. Practicing Medicine will be like working for a company — no more independence, no more freedom, and no more fun."

Disagreement

I happen to disagree with the substance and tone of these responses. I do not think we will have a comprehensive National Health Insurance Bill in the next ten years, nor do I believe the government will dramatically change, control, or spoil future physicians' careers.

Instead of NHI, I predict a limited catastrophic bill, which will take the politicians off the hook without hooking the U.S. Treasury. And I foresee a pluralistic health system — which liberals will undoubtedly label a disorganized, disorderly "nonsystem" — with a place for young physicians with talent, enterprise, and brains. Still, as a father of two sons, now eight and 15, I will advise them, should they choose Medicine, to acquire as much organizational, managerial, and leadership know-how as possible. For Medicine in the future will be made up of physicians within interdependent organizations. An exception to this may be the specialist, who may well continue to practice alone and within small groups of specialists.

Death of NHI

National Health Insurance (NHI) is neither inevitable or imminent. Indeed, NHI may be dead, and its mortal illness may have started in 1974. That year Senator Kennedy and Wilbur Mills, then Chairman of the House Ways and Means Committee, introduced a compromise NHI plan — the Comprehensive National Health Insurance Act. Mills held extensive hearings on the bill, but committee members could not agree on administration and financing. Mills dropped the hearings, and Congress is no closer now than then to consensus on basic principles of a NHI bill.

Other Opinions

I am not alone in my opinion about subsiding enthusiasm for an NHI bill:

- Jerry Prussin, a well-known Washington consultant on health care matters and Editor-in-Chief of *HMO and Health Service Report,* says: "Enactment of a comprehensive NHI plan is perhaps further from being a reality today than has been the case under the Nixon Administration. Immediate action on NHI is unlikely, and if any action is taken before the next presidential election, it will be severely limited in scope."[1]
- Peter Drucker, perhaps America's foremost social critic and social philosopher, notes: "The only reason, I suspect, that we still hear of 'National Health Service' is Senator Edward Kennedy's — understandable — desire to have his name on one piece of major national legislation. Even the unions who sign their names to the Kennedy proposal and testify for it, are at best lukewarm."[2]
- Eli Ginzberg, Columbia University Professor of Economics and 30-year veteran of the Health Care Wars, concludes: "My present assessment is that the odds favor no early passage of NHI — after all, it has been around since 1912 — primarily because the budgeting and tax considerations will not be politically solvable. But even if a consensus is achieved, the only type of NHI likely would be a modestly financed 'catastrophic illness' coverage, which would leave the present system largely intact."[3]
- Finally there is Alain Enthoven, HMO and Consumer Health Plan enthusiast, Professor of Public and Private Management at Stanford Business School, and former consultant to Joseph Califano. He dismisses Kennedy's Health Security Program as managerially impractical and politically impossible with these words: "The government is simply incapable of managing the Health Security Program. It does not have the organization, and it cannot acquire the management capability on a sustained basis . . . When it becomes clear what doing an effective job means, e.g. closing excess beds in some areas to pay for needed beds in others, and Board members start feeling the wrath of citizens expressed through their Congressmen, and seeing the implementation of their plans tied up in court, the two-year turnover in assistant secretaries in the Departments of Defense and Health, Education, and Welfare is sure to emerge."[4]

Two Choices

If an NHI bill fails to pass, what will happen? If the present rate of health care inflation continues — i.e. the voluntary efforts of the American Medical Association, the American Hospital Association, and Blue Cross, Blue Shield and other third parties providers fail — Walter McClure of InterStudy in Minneapolis thinks we have two choices: (1) restructuring the private system to establish effective market forces; or (2) turning the whole thing over to government to regulate.[5] McClure, and Paul Ellwood, President of InterStudy, endorse strong private restructuring, and point proudly to the performances of HMOs and competing health plans in the Twin Cities:

TABLE
Expansion of Twin Cities HMOs.*

Year End	Number of HMOs	Members	Percent Increase
1970	1	36,000	81%
1972	3	55,000	52%
1974	6	83,000	51%
1976	7	145,000	75%
1978	7	256,000	77%

---

*Source: *Minneapolis Tribune*, March 4, 1979

Just last week, about 400 of 700 private practitioners in Ramsey, Dakota, and Washington counties announced they were forming yet another HMO: The Metropolitan Area Prepaid Plan. And, as *Minnesota Medicine* readers learned last year from an interview with Richard Simmons of the Physicians' Health Plan of Greater Minneapolis, the idea of a cooperative health plan among private physicians, properly controlled, works and is profitable.[6] In the March 4, 1979 *Minneapolis Tribune,* Ellwood is quoted as saying: "It is clear that this is the only community (in the nation) where we have the majority of the medical profession and hospitals locked in this kind of competition. We have here a health system being subjected to a lot of economic, social, and market forces that have never occurred in the health system before."[7]

Unwise Extrapolation

Ellwood's assessment is probably correct. But to extrapolate the Twin Cities experience to the nation as a whole would be unwise. Minnesota physicians, on the average, are five times more likely to practice in groups than physicians in the rest of the U.S. For many of us, to join an HMO or an Independent Practice Association (IPA) is not a radical step. But for physicians elsewhere, competitive health plans are a large adjustment.

I recall a Texas politician's reply to then Senator Mondale, who had just said that on-site voters' registration worked well in Minnesota, so it would work well anywhere. The Texan replied: "Senator, comparing Minnesota politics to Texas politics is likening a church pew to a bordello."

Although McClure's and Enthoven's scheme for interlocking competing Consumer Health Plans may well work in a state like Minnesota, I am deeply skeptical that most physicians or most patients will accept this concept elsewhere. This is a huge and diversified country — with different traditions, perceptions and expectations in each region. I believe, with Drucker: "The bulk of health-care delivery 10 years hence will still be with the private physician, though more and more will be in what are (erroneously) called group practices. Next in importance will be the IPA. Employers in certain areas will get together and set standards and fees for medical services. The HMO, on the other hand, will grow only to the extent to which government imposes it."[2]

Minnesota, as I have noted, may not follow the national trend. Here health planners project HMOs may "capture" 30 to 40 percent of the metropolitan population, and a smaller percent of the rural population.

Ginzberg Scenario

Of the scenarios for the next ten years that I have read, I am most inclined to go along with Professor Ginzberg's, as expressed in the October 1978 *Annals of Internal Medicine* under the title: "How Much will U.S. Medicine Change in the Decade Ahead?"

I trust Ginzberg's analysis and judgment for three reasons: (1) he has a keen sense of power relationships, i.e. in his book *Limits of Health Reform*[8], he points out no national bill can be enacted if physicians, hospitals, and health insurance plans flatly oppose the bill; (2) he strikes me as a neoconservative, which is usually defined as a disillusioned liberal with common sense and a grasp of reality: and (3) he bases his predictions on what has actually happened since Medicare, rather than what he wishes would be.

For an example of wishful liberal thinking, I offer the following excerpt from the *American Journal of Public Health,* by Doctor Milton Terris, Professor of Community and Preventive Medicine at New York Medical College: "In the industrial capitalistic countries with well entrenched health insurance systems — in which practitioners are essentially small businessmen selling their services — resistance to change to a salaried service is very great. Nevertheless, the trend is unmistakably toward the national health service. The latter has demonstrated not only its superiority in terms of quality and health effectiveness, but has shown that it is unnecessary to submit to the blind forces of the medical marketplace; nations can plan rationally for their health services and can plan them well.''[9]

Ginzberg looks at the performance of government with a more jaundiced and critical eye. According to him, these are the noteworthy developments that have occurred since Medicare: (1) great increase in use of health-services by low-income families, with the poor now seeing physicians more often than members of middle and upper classes; (2) significant expansion in nursing home care — from 569,000 beds in 1965 to 1,407,000 beds now (a 150 percent jump); (3) ''striking infusion'' of new dollars into the health system — from $39 to $180 billion (a 4½ fold increase); (4) ''striking increase'' in number of people employed in the health system — from 3.7 to 5 million (a 60 percent increase compared to a population growth of 13.5 percent); and (5) a marked expansion of government ''intervention'' into all aspects of Medicine.

Ten Year Forecast

From these historical factors, from the present cost containment fervor, from public uncertainty whether it wants NHI *if* forced to pay heavy taxes, and from increasing public awareness of the limits of any health care system, Ginzberg forecasts these changes in Medicine in the next decade: (1) consolidation rather than expansion of the present system, particularly in the hospital sector (''By 1990, a great many hospitals are likely to be reduced to a state of genteel poverty''; (2) absorption into the system of the greatly increased supply of new physicians, which may ease the ''maldistribution'' problem; (3) more escalation of costs with both government and third parties imposing regulations to slow down these cost rises: (4) the ''unlikelihood'' of any National Health Bill; and (5) more recognition by the public of the limitations of medicine in improving their lives.

Cautionary Note

In closing, a cautionary note. Socioeconomic forecasting is a little like weather forecasting. Do clouds of the horizon mean a storm, or will they blow over and uncover blue skies? Only one thing is certain: you cannot predict the weather nor the future. I do think a centralized comprehensive HEW-administered National Health Plan is dead. This does not mean some other ''comprehensive'' plan, perhaps administered by private providers and where employers pay a significant portion, might not come. But in a highly developed country like the United States — with strong and competing interests, with a tradition of debate, with adversarial checks and balances, and with considerable governmental inertia on controversial issues — I believe a mixed system of health care, which will give citizens equal access and protection, is more likely to evolve.

Richard L Reece MD

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Cholelithiasis in a Child without Hemolytic Anemia

MICHAEL J. WEINER, M.D.*

A two-and-a-half-year-old girl presented with recurrent urinary tract infections and a pyelogram showed right upper quadrant opacities. Her gallbladder was later removed and had stones. The case is unusual because it occurred in a child and because the infant had no evidence of hemolytic anemia — the usual case of cholelithiasis in childhood.

CHOLELITHIASIS IN children, and especially in very young children, is generally considered by most physicians to be a very rare occurrence and usually associated with hemolytic anemia. Indeed, Caffey states, "Prior to puberty, opaque biliary calculi are extremely rare . . . should raise the question of familial (spherocytic) anemia, because they are found most frequently in this condition."[1] There is, however, much evidence in the literature to indicate that these assertions are unfounded. The radiologist should be aware of the importance of cholecystitis and cholelithiasis in children when examining the abdomen.

Case Report

A 30-month-old white girl was admitted for workup of recurrent urinary infections. An intravenous pyelogram revealed several small opacities in the right upper quadrant in the region of the gallbladder (Figure). Cholecystography was performed and non-function of the gallbladder was noted. An underlying cause for gallstones was considered.

Family history showed that the mother had been hospitalized briefly while in the first or second grade for an acute problem which required blood, plasma, and fluids. The details were not well recalled, and the episode was self-limiting with no subsequent attacks. The mother had persistently heavy menses and remained chronically anemic. Peripheral blood smears of the mother allegedly revealed spherocytes. The father's history was essentially negative.

The child's hemoglobin on this admission was 10.2 with hematocrit 32, and a normal white count. Spherocytes were allegedly seen in her peripheral smear. Hemoglobin electrophoresis revealed a normal adult hemoglobin pattern with no F hemoglobin. Fragility studies on fresh blood were normal. Even so, a provisional diagnosis of spherocytosis was made. The child was doing well, and further treatment was temporarily deferred.

The family moved shortly thereafter to a large city where the child was seen at a major medical center for evaluation of her anemia and possible need for splenectomy. Work-up in the hospital there failed

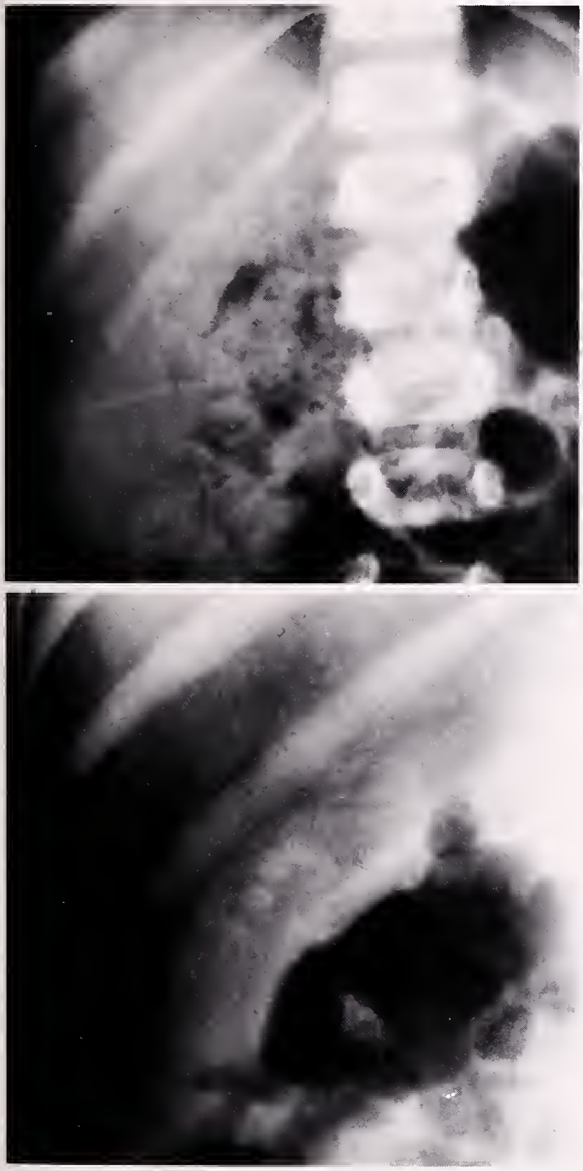

Figure — A supine view of the abdomen (A-top) and a coned view of the right upper quadrant (B-bottom) show several opaque gallstones.

---

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See editorial, page 253.

to confirm the diagnosis of hereditary spherocytosis. Her mild anemia had resolved, and the reticulocyte count was only minimally elevated. Osmotic fragility of the red cells with and without incubation was normal. Red cell G-6-PD and pyruvate kinase levels were normal. Haptoglobin was normal. It was concluded there that the child did not have spherocytosis or other significant hemolytic disease, and splenectomy would not be necessary. A cholecystectomy was performed during the same admission. Several pigmented gallstones were found in the gallbladder without significant inflammatory changes of the gallbladder mucosa.

After discharge the T½ of the patient's red cells was measured with chromium tagging. T½ equalled 23.7 days, the normal range being 28-35 days. It was felt that this slightly shortened life span of the red cells, in view of the lack of significant anemia, did not warrant studies.

The child was seen once more a year later for follow-up. She was well, and CBC, platelets and reticulocyte count were normal.

Discussion

Since the first case report of cholecystitis in a child in 1723 by Gibson, there have been over 1200 cases of biliary disease in children reported. The majority of these patients did not have associated hemolytic crises.[2] Strauss[5] reported thirteen cases of cholelithiasis in children from ages three to 17 years and reviewed 129 more cases from the recent literature. Of these 142 cases only 18 had evidence of hemolytic disease. Johnson[2] has since reported 13 additional cases of cholelithiasis and cholecystitis in children ages four to 18 years of which only three had probable hemolysis; all three of these had sickle cell disease. Etiologic factors concerning stone formation in all these patients, besides hemolysis, included an association with a family history of biliary disease, liver disease, cholecystitis, malformations such as bile duct stenosis and diverticulum, previous abdominal surgery, hypercholesterosis, and abdominal or genitourinary infection. The relationship of these associated factors did not often define a precise mechanism of calculus formation, serving to show that the etiology of cholecystitis, and cholelithiasis in children is as uncertain as in adults.

Our case is interesting for several reasons: (1) The child was two and a half years old at the time of diagnosis. Though many cases of cholelithiasis have been reported[2,3,5] in infants and young children, even on occasion in the fetus,[4] this case is at the lower limits of age incidence. (2) The diagnosis of cholelithiasis was made from a plain film of the abdomen and confirmed by cholecystography. The possibility of biliary disease, especially in the child with abdominal pain, should always be entertained by the radiologist. (3) There was no conclusive evidence of hemolysis and no significant anemia. Yet a presumptive diagnosis of spherocytic anemia was made, abetted no doubt by a desire to explain the gallstones. This diagnosis was later abandoned after extensive testing. This case illustrates the fact that hemolytic anemia should not be the prerequisite for the consideration of gallstones in children, a fact confirmed by a perusal of the literature. (4) It is also interesting that this child had recurrent urinary infections, an association noted by Strauss in four of his thirteen new cases, and in several of those cases he reviewed. The etiological significance of this, if any, is not clear.

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John J. Wild, M.D.

Dr. John J. Wild received the Pioneer Award from the American Institute of Ultrasound in Medicine at its meeting in San Diego, California last October.

The award recognized Dr. Wild's founding scientific discoveries which he carried out at the Wold-Chamberlain Navy Base in the spring and summer of 1949. In November 1949 Dr. Wild authored an historic paper entitled "The Use of Ultrasonic Pulses for the Measurement of Biologic Tissues and the Detection of Tissue Density Changes", which was published in SURGERY and is now considered the primary reference on the subject of pulse-echo ultrasound in medicine.

Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage

KENTON BODILY, M.D.,* and RONALD P. FISCHER, M.D.*

Two cases of aortic rupture and three cases of right ventricular rupture following closed chest cardiac massage were observed among 2,659 autopsied patients during an eight-year period. All five patients sustained multiple thoracic cage fractures as the result of closed chest cardiac massage. In four of the five patients, cardiac resuscitation was attempted using mechanical cardiac resuscitational devices.

Iatrogenic injuries, dominated by thoracic cage fractures, which are frequently induced by closed chest cardiac massage may thwart resuscitational efforts, and, most certainly, increase the post-resuscitational morbidity among survivors. Fortunately, aortic and ventricular rupture has been only rarely reported following closed chest cardiac massage (aortic rupture — 2, right ventricular rupture — 4, left ventricular rupture — 1). The iatrogenic injuries induced by closed chest cardiac massage result from overzealous sternal compression and by compression applied too high on the sternum or to either side of the sternum. An awareness of the ease with which iatrogenic injuries can be induced during closed chest cardiac massage coupled with close observation of the technical details of closed chest cardiac massage can best minimize these complications. Our experience indicates that particular caution should be taken when using mechanical cardiac resuscitational devices.

IATROGENIC INJURIES induced by closed chest cardiac massage result mainly from over zealous and/or improperly applied sternal compression or from the improper use of mechanical compressional devices and they are, in large part, preventable. Nevertheless, iatrogenic injuries, dominated by thoracic cage fractures, are frequently induced by closed chest cardiac massage (Table).[1] These injuries increase post-resuscitational morbidity and may thwart resuscitation. On rare occasions, the fatal complications of aortic rupture and myocardial rupture occur during closed chest cardiac massage. Two instances of aortic rupture and three instances of myocardial rupture resulting from closed chest cardiac massage were documented among 2,659 autopsied patients in Saint Paul-Ramsey Hospital during an eight year period (1967-1974). Approximately one-third to one-half of these patients had undergone closed chest cardiac massage; thus, aortic rupture or myocardial rupture occurred in approximately 0.4-0.6 percent of the patients who died following closed chest cardiac massage.

Aortic Rupture

Rupture of the thoracic aorta occurred in two patients. Neither rupture occurred in an area of cystic

TABLE

Iatrogenic Complications of Closed Chest Cardiac Massage — Autopsy Materials*

rib fractures	28-80%
sternal fractures	2-47%
pneumothorax	3-20%
hemothorax	3-20%
hepatic injury	2-19%
splenic injury	0.3-10%
superficial myocardial injury	13-16%
bone marrow emboli[7]	91%

*Modified from reference #1

---

*Department of Surgery, Saint Paul — Ramsey Hospital, Saint Paul, Minnesota, and the Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota.

This study was supported by The Saint Paul — Ramsey Hospital Medical Education and Research Foundation.

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Dr. Fischer presently at Keno Community Hospital, Department of Surgery, Tuscon, Arizona.

See editorial, page 257.

medial necrosis. Mechanical cardiac resuscitational devices were used on both patients, and both sustained sternal and multiple, bilateral rib fractures. One patient, who had a rupture through an atherosclerotic plaque at the root of the aorta, died of a cardiac tamponade. The other exsanguinated from a linear rupture of the descending aorta at the level of the left mainstem bronchus.

Right Ventricular Rupture

Three patients incurred rupture of the anterior right ventricular wall in an area free of myocardial necrosis. In each, the pathologist deemed the rupture to be secondary to myocardial penetration by rib and/or sternal spicules. Mechanical cardiac resuscitational devices were used on two patients. All three patients sustained multiple thoracic cage fractures. One had a bilateral fracture of the third through seventh ribs, one had multiple, bilateral rib fractures and a sternal fracture, and one had a sternal fracture at the level of the fourth intercostal space.

Discussion

In 1965 Nelson and Ashley[2] reported a case of fatal cardiac tamponade from a nearly circumferential aortic rupture three centimeters above the aortic valve in a patient who had sustained an overlying sternal fracture and fractures of the second, third, and fourth ribs in the midclavicular line. Patterson, Burns and Jannotta[3] reported one patient with eight rib fractures who exsanguinated from a one centimeter rupture through an atherosclerotic plaque of the anterior, proximal descending aorta and another patient in whom a mechanical resuscitational device had been used but who did not incur thoracic cage fractures. This patient sustained a fatal hemopericardium and a hemomediastinum from rupture of the ascending aorta six centimeters distal to the coronary ostei.

Three cases of ventricular rupture have been previously reported by Agdal and Jorgensen.[4] Two patients with right ventricular rupture had a myocardial infarction distant to the site of ventricular rupture. The third patient did not have a myocardial infarction. All three patients had multiple rib fractures, and one also had a sternal fracture. One patient with right ventricular rupture and one patient with left ventricular rupture had myocardial penetration by rib spicules. However, in the third patient, who had a right ventricular rupture, the rib fractures were remote from the site of rupture. Baldwin and Edwards[5] reported two cases of right ventricular rupture in which they postulated that these ruptures resulted from increased right ventricular pressure. They surmised that a massive pulmonary emboli prevented right ventricular emptying in one patient and that excessive external pressure placed too high on the sternum occluded the right ventricular outflow track in the other patient. In both patients, the right ventricular rupture occurred at the ventricular apex rather than the anterior ventricular wall as observed in Agdal and Jorgensen's patients and in our patients.

Except for the case of the left ventricular rupture reported by Agdal and Jorgensen, rupture of the left ventricle has not been convincingly reported to result from closed chest cardiac massage. Left ventricular rupture does occur, however, in approximately ten percent of patients dying after an acute myocardial infarction.[6] Many of these patients have undergone closed chest cardiac massage; however, their left ventricular ruptures are not believed to relate to closed chest cardiac massage, but rather are believed to occur spontaneously through areas of transmyocardial necrosis. During the eight years of our review, 11 patients who had received closed chest cardiac massage had left ventricular rupture. In each, the rupture occurred in an area of pre-existing transmyocardial necrosis and these left ventricular ruptures were judged, therefore, not to relate to the closed chest cardiac massage.

During closed chest cardiac massage, depression of the lower third of the sternum to a depth of four to five centimeters compresses the heart between the thoracic spine and sternum forcing the ventricular blood into the pulmonary and systemic circulations. Upon sternal release, the elastic recoil of the thoracic cage creates a negative intrathoracic pressure, which permits cardiac refilling. Positioning of the hands on either side of the sternum promotes rib fractures, whereas placement of the hands too high on the sternum promotes sternal fracture. Thoracic cage fractures decrease the thoracic cage's compressional resistance permitting excessive cardiac compression. Thoracic cage fractures also decrease the elastic recoil of the thoracic cage generated by sternal release, thus, decreasing the negative intrathoracic pressure and venous return to the heart. These two circumstances, because they decrease the effectiveness of cardiac massage, may thwart resuscitational efforts.

Mechanical compressional devices were used on both of our patients with aortic rupture and two of the three patients with right ventricular rupture. These devices have several practical limitations which may be implicated in the production of iatrogenic injuries.

Because they are cumbersome, they are somewhat difficult to position properly over the lower one-third of the sternum. If they are not positioned properly, or if they are not repositioned after defibrillation, or if proper positioning is not maintained during patient transport, the incidence of thoracic cage fractures, and thus injuries to other organs, is increased.

Although in our experience mechanical compressional devices are culpable in producing right ventricular and aortic rupture following closed chest cardiac massage, other iatrogenic injuries most frequently occur as the result of over zealous resuscitational attempts. Our observation has been that when cardiopulmonary resuscitation is not promptly achieved, continued resuscitational efforts result in over zealous sternal compression. This was illustrated recently during a retraining session with the resusci-Anni model when one of the students commented, "it just doesn't seem the same when you don't hear the ribs break."

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Continuing Medical Education

Minnesota Society of Clinical Pathologists

Spring Meeting: Saturday, April 21, 1979

Symposium on Hematopathology:

1. "Serum Ferritin — Use and Interpretation in the Diagnosis of Iron-Deficiency States" by Dr. Virgil Fairbanks, Mayo Clinic.
2. "Monitoring Heparin Therapy in DIC and Other Diseases" by Dr. Francis Kazmier, Mayo Clinic.
3. "Membrane Surface Markers in Lymphocytic Leukemias" by Dr. Richard Brunning, University of Minnesota.
4. "Pre-Leukemia" by Dr. Robert Pierre, Mayo Clinic.
5. "Recent Advances in the Diagnosis of Malignant Lymphoma" by Dr. Glauco Frizzera, University of Minnesota.

University of Minnesota — Health Sciences Building A, Room 2690. Approved for CME #I Credits, 5 Hours. Contact: Dr. Charles Horwitz, Mt. Sinai Hospital, Minneapolis.

Mayo Clinic

The Department of Pediatrics of the Mayo Clinic is sponsoring Pediatric Days, April 27-28, 1979, in Rochester, Minnesota. The program theme is "Health Problems in the Adolescent" and faculty will consist of Mayo Clinic Pediatric Staff and specialists from other departments. The Amberg-Helmholz Lecture will be given by Dr. Michael I. Cohen, Department of Adolescent Medicine, Albert Einstein School of Medicine.

Inquiries can be directed to the Program Director, Robert H. Feldt, M.D., Professor of Pediatrics, Mayo Medical School, Rochester, Minnesota 55901.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*. Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
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References: 1. Citations available on request – Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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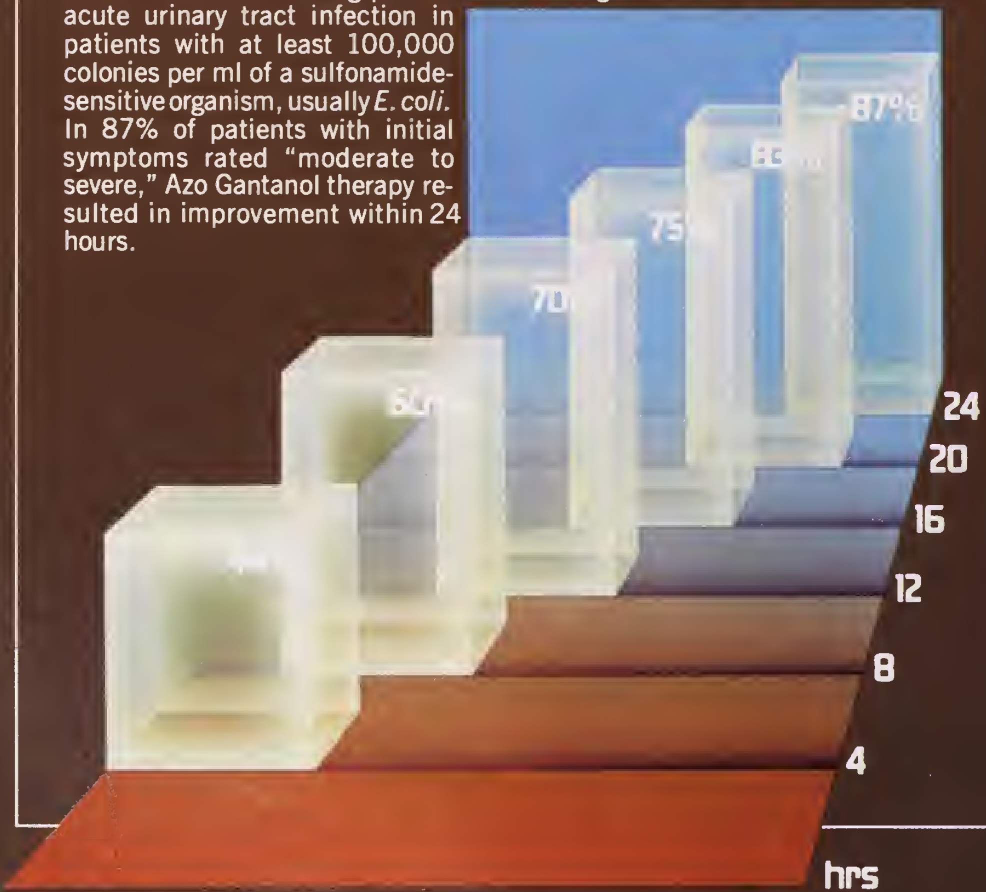

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tests with bacteriologic and clinical re
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the usefulness of antibacterials inclu
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disturbances.

Warnings: Safety during pregnancy no
Deaths from hypersensitivity reaction
tosis, aplastic anemia and other blood
have been reported and early clinical
throat, fever, pallor, purpura or jaundi
dicate serious blood disorders. Freque
urinalysis with microscopic examinati
ommended during sulfonamide thera

Precautions: Use cautiously in patient
paired renal or hepatic function, seve
bronchial asthma; in glucose-6-phosp
dehydrogenase-deficient individuals i
dose-related hemolysis may occur. M
adequate fluid intake to prevent cryst
stone formation.

Adverse Reactions: *Blood dyscrasias* (
ulocytosis, aplastic anemia, thromboc
leukopenia, hemolytic anemia, purpur
thrombinemia and methemoglobinemi
reactions (erythema multiforme, skin
Stevens-Johnson syndrome, epiderma
urticaria, serum sickness, pruritus, ex
dermatitis, anaphylactoid reactions, p
edema, conjunctival and scleral inject
sensitization, arthralgia and allergic m
G.I. reactions (nausea, emesis, abdo
hepatitis, diarrhea, anorexia, pancreat
stomatitis); *CNS reactions* (headache,
neuritis, mental depression, convulsio
hallucinations, tinnitus, vertigo and in
miscellaneous reactions (drug fever, c
nephrosis with oliguria and anuria, pe
nodosa and L. E. phenomenon). Due
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Micropolycystic Liver

Occurring in an Adult with Gluten Enteropathy

C.E. WEIGENT, M.D.* and K.C. HANSON, M.D.†

A case is reported of a 48-year-old diabetic man who was diagnosed as having gluten enteropathy at age 34 years. Approximately one year prior to his death from acute myocardial infarction, an episode of gastrointestinal bleeding occurred. Esophageal varices were demonstrated radiographically. At autopsy, congenital hepatic fibrosis was diagnosed. Its association with gluten enteropathy appears to be coincidental.

MICROPOLYCYSTIC LIVER is not a disease entity but rather liver abnormalities making up part of a spectrum of fibropolycystic disease of the hepatobiliary system and kidneys. Liver abnormalities are fibrosis in portal zones, bile duct proliferation, and agenesis of tiny portal veins. This is often associated with portal hypertension and esophageal varices. Also renal tubular ectasia is a common finding. This case is reported because of the association of micropolycystic liver and gluten enteropathy.

Case History

The patient's first hospital admission was in 1960 at the VA hospital when he was 34 years old. He had had watery diarrhea for two and a half years with an associated weight loss of 10-15 pounds. He had had insulin dependent diabetes mellitus for eight years. His family history was positive only for rheumatoid arthritis (mother) and hypertension (father and brother).

The physical examination was normal. The following laboratory data were normal: CBC, BUN, ESR, urinalysis, albumin, globulins, serum calcium, serum phosphorus, LE cell prep, stool for ova and parasites, stool bacterial culture, PBI, and BSP. His serum carotene was 18 and 25 micrograms per deciliter (normal 75-300). Initial prothrombin time was 51% of normal, which with vitamin K improved to 100%. His serum cholesterol was 117 mg per deciliter. Fasting blood sugar was 169 mg per deciliter.

An upper gastrointestinal series revealed swollen mucosal folds in the duodenal bulb and a "malabsorption pattern" of the small bowel mucosa. A barium enema, cholecystogram, and sigmoidoscopic examination were normal.

Two small bowel biopsies were unsatisfactory for diagnosis. A presumptive diagnosis of gluten enteropathy was made and gluten was withheld from his diet. He responded to this diet with cessation of his diarrhea. He was maintained on 35 units of NPH insulin.

The second hospitalization was in April, 1971. He had not adhered well to a gluten free diet and now had weakness, fatigue, a 10 pound weight loss, and diarrhea. The only changes in his physical examination were several microaneurysms in the right optic fundus and a liver down 2 cm from the right costal margin. Laboratory data revealed a hemoglobin of 11.2 gm per deciliter, serum iron of 40 ugm per deciliter, with a binding capacity of 360 ugm per deciliter. His serum carotene was 27 ugm per deciliter, serum alkaline phosphatase 37 units (normal 4-17) and serum SGOT 85 units (normal 10-40). The remainder of his blood tests were normal. A fecal fat was normal. An upper gastrointestinal series was essentially normal. A small bowel biopsy showed villous atrophy (see pathology). The patient reinstituted his diet with an excellent clinical response.

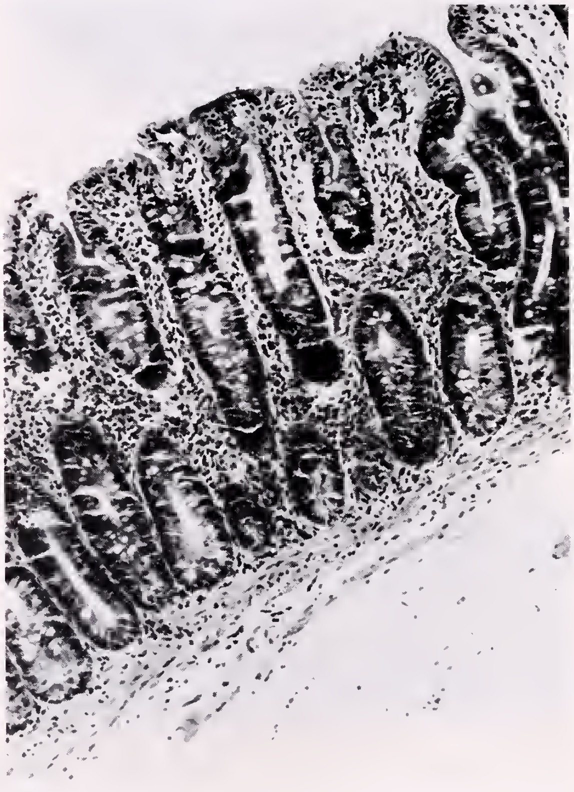

Fig. 1 — Severe villous atrophy and cellular infiltrate in lamina propria in small bowel biopsy (1971).

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See editorial, page 255.

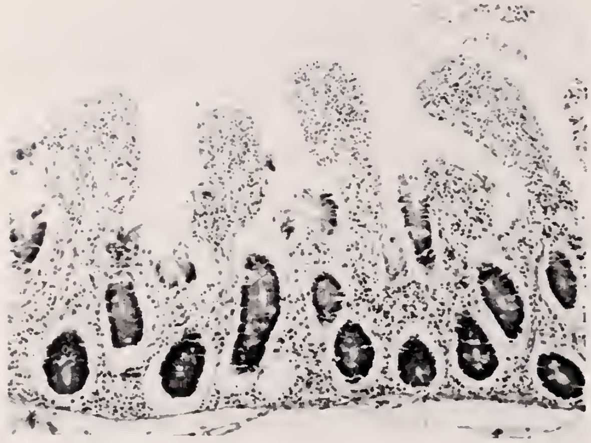

Fig. 2 — Small bowel (jejunum) at autopsy. Note villous pattern approaching normal.

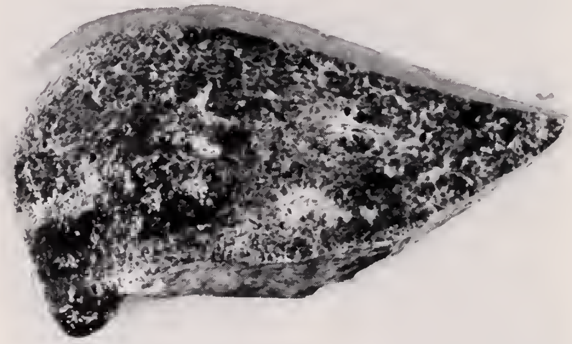

Fig. 3 — Cut surface of the liver showing prominent lobular pattern.

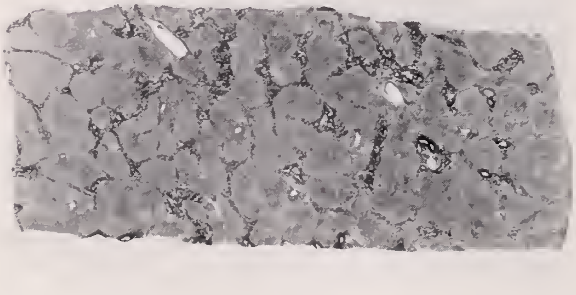

Fig. 4 — Liver parenchyma showing lobular pattern created by serpiginous fibrous septa with essentially intact lobular architecture.

The patient's third admission was in January 1974 because of hypoglycemic episodes. His blood tests were normal except for a BUN of 26 mg per deciliter and creatinine of 1.6 mg per deciliter. He had ⊩ protein in his urine. His blood pressure was 150/95 and microaneurysms were described in both eyegrounds. His hypoglycemia was controlled with decreased insulin doses.

His next admission was at another hospital in November 1974, for weakness, fatigue, and melena. His hemoglobin was 6.2 gms per deciliter on admission, his liver firm and 3 cm below the right costal margin. An upper gastrointestinal series revealed esophageal varices, endoscopy revealed large non-bleeding esophageal varices. A liver-spleen scan revealed slight enlargement of both organs with a mottled uptake over the liver. He was transfused and his bleeding ceased. Ascites developed during this hospitalization. Studies of the ascitic fluid were negative for micro-organisms and cytology.

His last admission to the hospital was in January 1975. He was transferred for evaluation of increasing visual problems, related to his diabetic retinopathy. On the evening of the day of admission he developed severe anterior chest pain, nausea, weakness, and shortness of breath. An electrocardiogram revealed an acute myocardial infarction and left bundle branch block. Chest Xray revealed pulmonary edema. The liver was enlarged and tender. He became hypotensive, developed episodes of ventricular tachycardia and expired on the day following his admission.

Pathological Findings

The small bowel biopsy (Figure 1) 1971 showed severe villous atrophy and moderately heavy cellular infiltrate in the lamina propria. Damage to the surface epithelium was evident. Paneth cells were prominent in the crypts.

The autopsy sections included a section of proximal jejunum (Figure 2). Despite post mortem loss of surface epithelium, a villous pattern approaching normal was found. The cellular infiltrate in the lamina propria was somewhat increased but the epithelial changes in the crypts were diminished.

The liver weighed 2,325 grams. The surface had an irregular grooved appearance. The parenchyma was very firm and the cut surface showed a prominent lobular pattern with lobules outlined by firm white tissue (Figure 3). A low power photomicrograph showed lobules outlined by increased collagenic connective tissue in portal areas (Figure 4). In many of the lobules central veins are evident. Normal central and no portal vein branches are seen (Figure 5) (see discussion). Varices were found in the lower one third of the esophagus. There were no ulcerations or evidence of gastrointestinal bleeding.

The spleen weighed 380 gms and showed chronic passive congestion.

The immediate cause of death was due to thrombosis of the left anterior descending coronary artery with an early acute anteroseptal infarct. The heart weighed 360 gms. The coronary arteries were severely atherosclerotic. The right lung weighed 910 gms. and the left lung

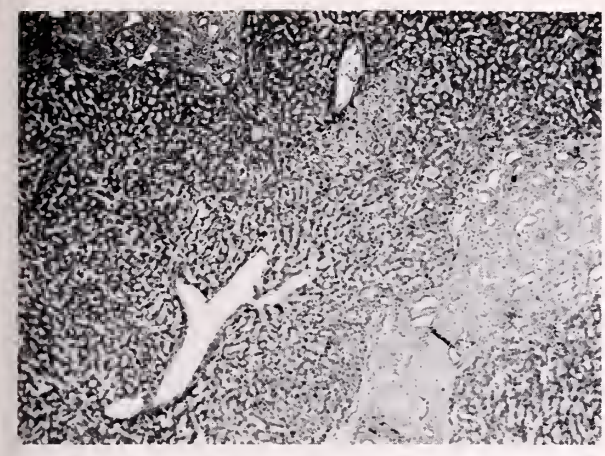

Fig. 5 — Portal areas showing increased collangenic connective tissue, increased numbers of normal bile ducts and absent portal veins. Note: normal central veins and arrangement of liver cells cords.

740 gms. They were edematous and congested. The kidneys weighed 190 and 185 gms. They showed diabetic glomerulosclerosis and arteriosclerosis. There were bilateral pleural effusions of 400 and 250 milliliters of clear straw colored fluid. The pancreas was of small normal size. Microscopically islets appeared decreased in number. There was mild irregular interstitial scarring and lymphocytic infiltration.

Discussion

Micropolycystic liver was first described in 1929.[1] In 1961 Kerr et al. called these findings congenital hepatic fibrosis.[2] Lately Sherlock has referred to it as micropolycystic liver.[3] Murray-Lyon et al.,[4] in a recent article, conclude that these liver findings are not a single pathological entity but abnormal findings in a spectrum of cystic diseases.

It has been known for some time that the findings of micropolycystic liver are sporadic in roughly 50% of cases and are associated with a type of renal cystic disease in somewhat over 50% of cases. These liver findings have been described with mixed cortical and medullary cystic renal diseases,[4] choledochal cyst,[2] with Caroli's syndrome,[4,5,6] and as an isolated anomaly.[7]

Many of the reported cases have been diagnosed in the first decade of life. Murray-Lyon et al.[4] considered five groups: Perinatal, neonatal, infantile, juvenile, and post-juvenile. Cases can first become symptomatic[6,8,9] later in life, like the patient in this report (age 48). Other patients are first found at autopsy to have micropolycystic liver. The patient in this report was noted to have polycystic liver only after death. This was an isolated finding in the cystic disease spectrum as his kidneys only showed diabetic changes.

Hepatocellular function is preserved because hepatic lobules surrounded by fibrous tissue are normal. Liver biopsy, often an open wedge biopsy, is necessary to make the diagnosis. Diagnosing micropolycystic liver is important for the following reasons. (1) With portal hypertension, porta-caval shunt may provide a permanent cure. (2) It may lead to the diagnosis of associated renal disease when present. (3) It may lead to the diagnosis of micropolycystic liver or associated conditions in family members. The association of micropolycystic liver with gluten enteropathy appears to be coincidental.

Summary

A case of micropolycystic liver not diagnosed during life is reported in a 48-year-old man with gluten enteropathy. The patient had diabetes mellitus with associated nephropathy. Death was due to myocardial infarction.

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Minnesota Medical Association
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Acute Viral Myocarditis

Clinical and Histologic Changes

C. M. BANDT, M.D.*, N. A. STALEY, M.D.† and G. R. NOREN, M.D.‡

Viral myocarditis appears to exist much more frequently than is apparent by clinical diagnosis. Individuals with myocarditis also appear to be at considerably higher risk for sudden and unexpected death. This paper presents three such cases of sudden unexpected death in individuals with histologic evidence of undiagnosed viral myocarditis. The variations in the natural history of the clinical disease is presented. Because of the difficulties in establishing other than a presumptive diagnosis, various diagnostic criteria are discussed.

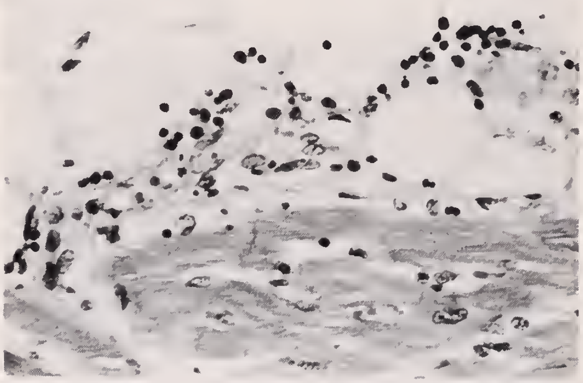

Fig. 1 — Photomicrograph of the left ventricular myocardium from an 11-year-old boy who was found unresponsive lying face down in two feet of water in front of his family's lakeside home. Past medical history was unrevealing. At necropsy, microscopic examination of the heart revealed the only potential cause of sudden death. This section demonstrates interstitial mononuclear cell infiltrates in association with pericarditis. (Hematoxylin and Eosin)

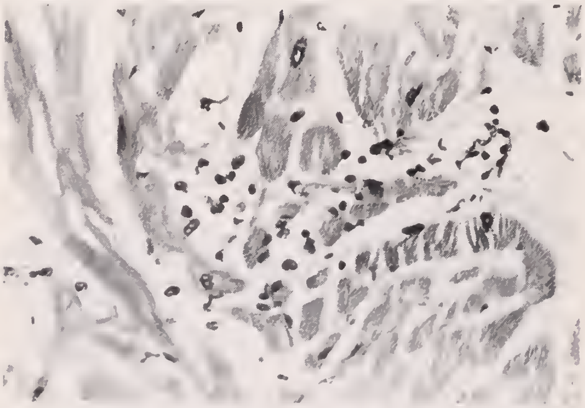

Fig. 2 — Photomicrograph from the myocardium of a 15-year-old boy who died suddenly and unexpectedly during an interscholastic wrestling match. The boy was stated to be in excellent health prior to his sudden demise. The only significant findings at necropsy were limited to the heart. The heart was grossly enlarged and on microscopic examination, focal areas of interstitial mononuclear cells were observed as demonstrated. (Hematoxylin and Eosin)

SUDDEN UNEXPECTED DEATH in individuals between the ages of one and thirty years is a relatively rare event. However, when it does occur, acquired inflammatory disease of the heart should be strongly considered as a potential cause of death.

In a recent three-year study of 353 pediatric deaths, age zero to 17 years, that were reviewed by the Hennepin County Medical Examiner's Office, a significant number (17%) of children dying a sudden and unexpected death were found to have myocarditis.[1] A total of 115 children died suddenly and unexpectedly by history and of those, 90 had cardiac tissue available for histologic examaination with 15 demonstrating interstitial myocarditis. Eight of the cases with myocarditis appeared in the birth to one year

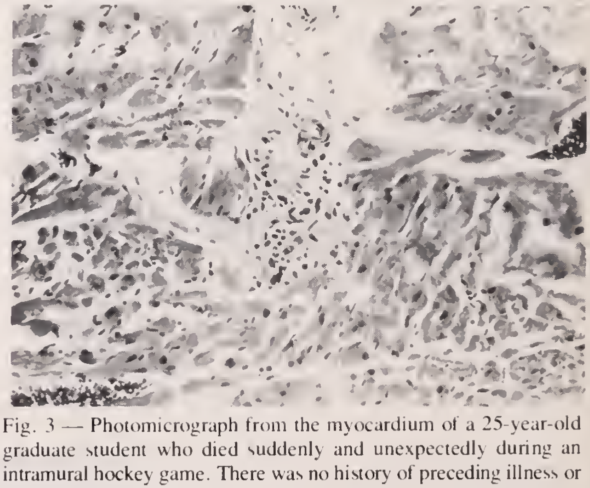

Fig. 3 — Photomicrograph from the myocardium of a 25-year-old graduate student who died suddenly and unexpectedly during an intramural hockey game. There was no history of preceding illness or injury. Histologic examination of the heart revealed small focal areas of interstitial mononuclear infiltrates. (Hematoxylin and Eosin)

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See editorial, page 253.

age group (eight of 79), while seven were over one year of age (seven of 11), Okuni's observation of ten cases of histologic myocarditis among 47 sudden deaths in school children (21%) is supportive of the Hennepin County study.[2]

In contrast, of 214 children dying a violent death (accident, homicide, or suicide) in the Hennepin County study, 48 had myocardial tissue available for study and only two of the 48 (4%) had histologic findings of myocarditis. Both of these children were over one year of age. This incidence is similar to Gore and Saphir's review of 40,000 autopsies in which they identified 1,402 cases of myocarditis for an overall prevalence of 3.5%. Stevens, in addition, has suggested that asymptomatic focal myocarditis in British males age 18 to 50 years, may be as high as 5%.[4]

Therefore, with the knowledge that myocarditis is present in a substantial number of the population at any one time, it is quite reasonable to expect that given the proper location within the myocardium, a fatal arrythmia could be precipitated and that massive involvement of the heart is not necessary to produce death.[5-9] However, unless there is monitoring of the cardiac events prior to death, the exact mechanism for sudden collapse does remain speculative.

The following cases are examples of sudden and unexpected deaths in children and young adults. In each, significant findings were limited to the heart with interstitial myocarditis observed in all three (Figures 1-3). Bacterologic and toxicological findings were unrevealing in each case.

Although the myocarditis in each of the three sudden and unexpected deaths presented here may represent examples of "incidental" myocarditis such as observed by ourselves and others in violent deaths and routine necropsies, inflammatory disease of the heart must be considered as a possible etiologic factor leading to the death of these individuals.

Etiology

Myocarditis has been produced by almost all agents known to afflict mankind though the bulk of myocardial inflammatory disease remains submerged by the more overt-expression of the infectious process. The viral agents which have been implicated in myocarditis are numerous. The most predominant ones are Coxsackie A and B virus, influenza virus, ECHO virus, mumps and rubella virus.

Grist and Bell reviewed 385 patients with suspected heart disease and found that the Coxsackie Group B virus was associated with at least one-half of the cases of acute myocarditis.[10] In addition, Burch and co-workers found evidence of Coxsackie B antigen in the myocardium by immunofluorescent techniques in 30.9% of routine autopsy specimens and Helin et al. reported a 33% incidence of myocardial involvement in clinical Coxsackie B_1 viral infection.[11/12]

Histology

Myocarditis is usually defined as an inflammatory lesion, characterized by cellular infiltrates which are predominantly mononuclear. Infiltrates may be focal or diffuse and show predilection for subendocardial or subepicardial regions. Myocytolysis and necrosis are varied and are dependent on the agent involved. Subepicardial foci are often associated with pericarditis. Lesions are usually not only limited to the interstitium and muscle, but may also involve specialized tissue, such as the conduction system. Localization as well as the extent of the lesion will be the determinant of functional impairment or clinical manifestations.

Miranda et al. in their study of Coxsackie B5 infection in mice showed that despite a mortality rate of greater than 50% at four weeks, very small foci of cellular infiltrates and necrosis involving only two or three muscle fibers were evident at three days after inoculation. Areas of necrosis increased in size and number, but never involved more than 12 or 15 fibers and by 15 days post infection, necrotic muscle was being resorbed, lesions were reduced in size, and fibrous tissue appeared.[13] Similar findings in mice affected with Coxsackie viruses A and B have also been observed by others.[14,15]

The subtle microscopic findings in acute viral myocarditis are further exemplified by Jaskiewica and Mrozinska[16] in which they described gross cardiac changes in mature female mice killed at 120 to 180 days after their nursing newborns were infected with Coxsackie B virus. The first observable changes were noted ten to fourteen days after the infection of the newborns and were characterized by discreet interstitial cellular infiltrates and eosinophilic staining of muscle cells in the mother's myocardium. Later these areas were replaced by histocytes and fibrous tissue. No calcific foci were noted. However, at 120 to 180 days, thin-walled left ventricles were noted with proliferation of the left ventricular endocardial cells in association with subendocardial fibrosis.

Natural History

Lerner and Wilson have reported several cases of acute myocarditis that have progressed to a chronic myocarditis or cardiomyopathy characterized by cardiomegaly and recurrent episodes of congestive heart failure.[17] It has been speculated that these cases represent an autoimmune phenomenon in which altered myocardial protein, virus, or viral-induced proteins may serve as a foreign protein to which specific heart reactive antibodies are formed. These antigen-antibody reactions occurring in heart disease could produce further damage to the myocardium.

The epidemiologic data presented earlier in this paper suggests that the vast majority of patients recover from their acute episode of myocarditis with little or no sequelae. Of those individuals surviving the initial illness, there are some who may retain evidence of myocardial damage, such as persistent conduction defects or cardiac hypertrophy and dilatation. At the other end of the spectrum are those patients who progress from their acute episode to a chronic cardiomyopathy with left ventricular endocardial proliferation and mitral valve insufficiency.

Viral Infections

Viral infections will usually have significant organ involvement other than the heart, and cardiac pathology may not be evident. In addition, there may well be an asymptomatic period following the initial phase of the viral disease before cardiac manifestations develop, thus diverting one's attention from an infectious etiology. The presence of persistent tachycardia out of proportion to fever, irregularities of the heart beat, presence of a gallop rhythm, dyspnea, or evidence of failure should alert the clinician to viral involvement of the heart. Weakness and fatigue are also common complaints in the older child. Cardiomegaly may not be present in mild cases, but when it does occur, the classic auscultatory findings of cardiomyopathies are usually present. These include atrial and ventricular gallops, accentuation and wide splitting of the pulmonic component of the second sound secondary to increasing pulmonary hypertension, and the presence of a systolic murmur of mitral and rarely tricuspid insufficiency. Premature beats of ventricular origin are common and atrial arrythmias also occur. Elevated erythrocyte sedimentation rates and elevation of AST (SGOT) and LDH levels are variably present, and are usually dependent on the nature of the infection and extent of the tissue damage.

Newborn Infant

Myocarditis in the newborn infant may be of a sudden onset during the first eight or nine days of life, sometimes preceded by a few hours or days with episodes of diarrhea and anorexia.[18] Clinical features include lethargy, facial pallor, and mild icterus. Tachycardia, dyspnea, and cyanosis if present early in the course, are evidence of cardiopulmonary failure. Cardiomegaly and hepatomegaly usually are present and electrocardiograms often demonstrate conduction defects and occasionally ST segment abnormalities.

Pericarditis will frequently accompany the myocarditis. In 42 adults with Coxsackie heart disease, Smith found that 20 had clinical pericarditis and 22 had myocarditis without evidence of pericarditis.[19] There was a predominance of male patients. Chest pain was present in 67% of patients with radiation to the throat, and relieved by sitting forward. Fever was present in 59% and 36% had flu-like illness with fever, malaise, lethargy, and sore throat.

Diagnostic Criteria

Lerner and Wilson have suggested criteria to establish the etiologic association of Coxsackie virus infection in patients with acute or chronic myocardiopathy and these criteria appear appropriate for most viral infections.[17] Higher order associations include isolation of the virus from the myocardium, endocardium or pericardial fluid. Moderate order association is present if virus is isolated from pharynx or feces or there is a four-fold increase in type specific neutralizing, hemaglutination inhibiting or complement fixing antibody. Moderate order association is also present if virus is isolated from the pharynx or feces with a serum titer of 1:32 or greater of type specific IgM neutralizing or hemaglutination inhibiting antibodies. Schmidt et al. have found that in initial infections with Coxsackie viruses, antibodies which appear early consist largely of 19-S immunoglobulins.[20-21] They are replaced by 7-S antibody globulins in the convalescent phase sera. Considerable cross reactivity of neutralizing antibodies occur among the Coxsackie B sera types and the possibility of demonstrating significant increases in neutralizing antibodies due to enteroviruses are greatly reduced if the titer in the acute phase is 1:32 or greater.

Therapy

Once the diagnosis of myocarditis is made, very careful observation of the patient, preferably in an intensive care setting, with adequate monitoring, is suggested, particularly if there is evidence of arrythmia, anginal-type pain, and cardiomegaly with or without congestive failure. Complete heart block may necessitate pacing, and strict attention to fluid administration should be maintained. Atrial flutter, atrial fibrillation, or failure may require digitalization which should be done cautiously. A lowered threshold for Digitalis toxicity in patients with myocarditis has been postulated, but not proven. Ventricular irritability may be treated with anti-arrythmic agents. They may, however, further depress myocardial contractility and should be used with caution.

Lim et al. described 10 patients, all below 30 years of age, who developed Stokes-Adams disease from complete heart block due to acute non-specific myocarditis.[22] Temporary transvenous pacing was instituted and in all except for two patients who developed permanent complete heart block, normal A-V conduction returned between 1-10 hours after ventricular pacing in seven patients and after 10 hours in the final patients.

The deleterious effect of exercise in experimental Coxsackie A and B myocarditis has been well established.[23] When mice are forced to swim in a pre-heated pool in the early infectious phase of this myocardiopathy, virulence is strikingly augmented and replication of Coxsackie virus in the heart is increased 530 times. For these reasons bedrest is recommended for the acute phase of the disease, which is usually limited to ten to fourteen days in viral infection. Studies by Pearce with experimental vaccinia in pseudo-rabies infections suggests that hypoxia increases both the incidence and severity of myocarditis.[24] Clinically, hypoxia plays a major pathogenic role in myocarditis in patients with influenza or poliomyelitis. Therefore adequate oxygenation is desirable, especially in the presence of pulmonary infiltrates, congestion or an irritable myocardium. Hyperbaric conditions, on the other hand, have also been shown to enhance replication of viruses.[25]

Kilborne demonstrated that when corticosteroids are given during the acute phase of Coxsackie virus Disease, both viral replication and myocardial necrosis are increased.[26] Rytel has suggested that cortisone may act by impairing the production of interferon and thus Lerner & Wilson have recommended that steroids be avoided at least during the first 10 days of infection.[27,17] Steroids may be considered if active disease continues or the patient is severely ill and unresponsive to usual therapies.

It is apparent that our current knowledge of the natural history of interstitial myocarditis is but the tip of a large iceberg. However, it is becoming increasingly apparent that this disease, which is produced by a myriad of agents, is responsive for a significant portion of the acquired cardiomyopathies and is probably one of the leading causes of sudden unexpected death in the older child and young adult.

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16.-27. May be secured from the author.

MMA Annual Meeting

The Minnesota Medical Association House of Delegates will meet Wednesday, May 16 and Friday, May 18 in St. Paul, Minnesota during the 1979 Annual Meeting of the MMA. Included on the agenda are Dr. Hoyt Gardner, Louisville, Kentucky, President-Elect of the American Medical Association, and Dr. George Pettersen, Minnesota Commissioner of Health. A major item to be considered by the delegates will be a report from the Commission on Health Care Costs of the Minnesota Medical Association.

Index to Advertisers

American Heart Association	282
Anderson, C. F. Co.	228
Army Reserve	282
Beltone Electronics Corporation	256
Brissman Kennedy	214
Burroughs-Wellcome Co.	248
Classified Advertising	286
Fidelity Professional Services, Inc.	278
Finley & Friday, Inc.	216
Health Central	260
Jimbos, Inc.	272
Lilly, Eli & Co.	258
Mead Johnson Pharmaceutical Division	251, 252
Medcalf Orthopedic Appliance Co.	282
Medical Protective Company	278
Merck, Sharp & Dohme	242
Merrell-National, Inc.	228, 229, 270, 271, 272
Metropolitan Medical Placement	262
Minnesota Medical Association	287
Purepac Pharmaceutical Co.	305
Roche Laboratories	Cover 2, 211, 212, 230, 238, 239, Covers 3, 4
Shattuck/Saint Mary's/Saint James	260
Smith, Kline & French	269
Trautmans	260
United States Air Force	204
Upjohn Company	240, 241, 242
Warner-Chilcott Co.	254

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Final classification of the less-than-effective indications requires further investigation.

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As with all anticholinergics, inhibition of lactation may occur.

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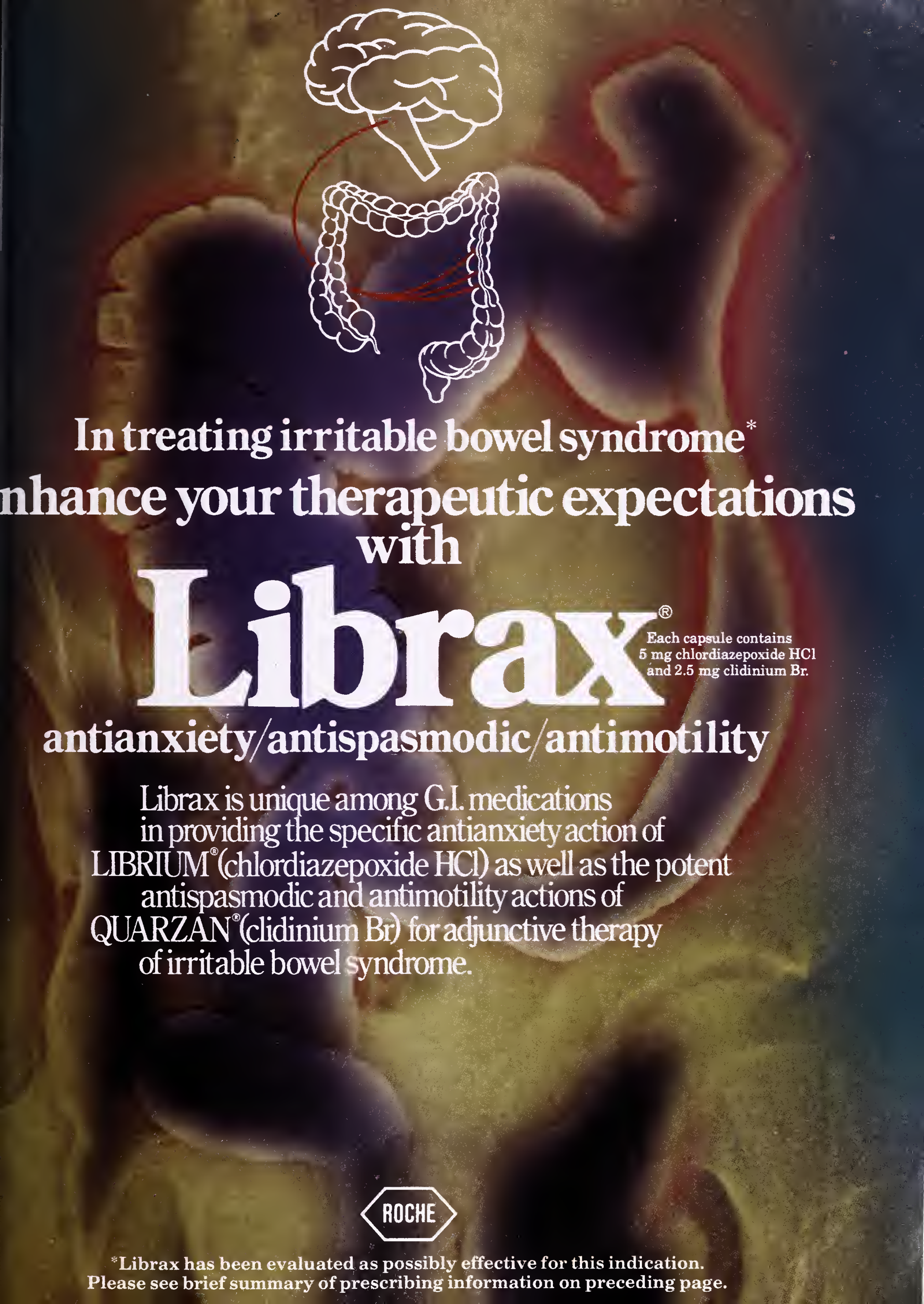

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*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

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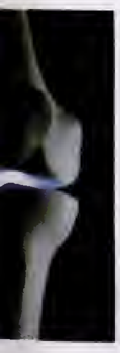

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The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
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Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.
Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.
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Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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An Adult Phenylketonuric with Schizophrenia

Clinical and Biochemical Similarities and Possible Genetic Connection between the Two Diseases

ROBERT O. FISCH, M.D.,* WILLIAM B. HOSFIELD, M.D.,† PI-NIAN CHANG, PH.D.,‡ JOHN BARRANGER, M.D.,# and DONALD W. HASTINGS, M.D.§

A 22-year old phenylketonuric man of borderline intelligence developed symptoms of schizophrenia: auditory hallucinations, withdrawal, and numerous delusions. Phenylketonuria and schizophrenia had occurred among members of the family. A diet low in phenylalanine failed to improve his symptoms. Limited data suggest a clinical, biochemical and possible genetic connection between the two diseases.

A POSSIBLE RELATIONSHIP between phenylketonuria (PKU) and schizophrenia may exist evidenced by the case of a 22-year old white man who developed symptoms of both diseases and who has a retarded, phenylketonuric, younger sister and a schizophrenic grandmother. The case raises the question of whether the two diseases may be linked biochemically/genetically or were simply coincidental in this patient.

The hypothesis that persons heterozygous for PKU are apt to suffer more from psychopathology than others was first suggested by Fölling.[1] A possible correlation between biochemical abnormalities and mental aberations was made by Wright and Tarjan,[2] in which they refer to psychotic behavior in PKU patients during childhood and later years manifested by withdrawal from reality, failure to relate to people, absence of emotional response (except fright) and the presence of echolalia and stereotyped, catatonic-like posturing. A prediction by Woolley in 1961 based on the serotonin hypothesis, predicted that schizophrenia will occur among phenylketonurics (PKUs).[3]

Perry et al. described a family with four adults, three females and one male, of normal intelligence.[4] Among the three females, two of them developed symptoms of schizophrenic psychotic episodes at 28 years of age. All four members of the family were previously unrecognized PKUs.

In light of the above observations, the presumed success of early treatment of PKU may be incomplete. Furthermore, the association of the disorders may be genetic or the result of the biochemical defect and thus beyond the scope of current management.

Case Report

The patient, a 22-year-old white man, the oldest of four children, was the product of a full-term, uneventful pregnancy and delivery. He sat up by eight months and walked by 15 months of age. His first word was used at age four and sentences at five years of age.

At age five, the diagnosis of PKU was made. His IQ was estimated in the 50-70 range and he received no specific treatment at that time. At age 12 a low phenylalanine diet was instituted for six months because of excessive hand tremors; he showed improvement while on the diet.[5] Since that time he has been followed yearly at the University of Minnesota Phenylketonuric Clinic. His IQ, measured by Wechsler Intelligence Scale for Children, was 77 at age 11 and at age 15. EEG records revealed excessive slowing at times with occasional spikes; however, on other records, no abnormalities were seen. The patient has had eczema and hand tremors dating back to the early teens. He has not had seizures. Past history was otherwise unremarkable.

The patient attended special schools and finally, a special vocational school until 19 years of age. He began working as a dishwasher and first noted auditory hallucinations, especially at night. In January, 1975, he began outpatient counseling with both individual and family evaluation sessions. A special diet low in phenylalanine was tried while he was at home, but was ineffectively maintained. He also showed irritability, considerable job dissatisfaction, difficulties with sleeping and considerable social withdrawal. Imipramine was prescribed by a private physician. Due to increasing hallucinations, he was hospitalized in July of 1975 for two months at the University of Minnesota Hospitals.

Family History

The father, 58-years-old, in good health, dropped out of high school in the 10th grade. His mother (the patient's grandmother) lived an active life but began having auditory hallucinations in her mid-forties, was suspicious of people, anxious and had delusions. She was withdrawn and was hospitalized many times with the diagnosis of schizophrenia, paranoid type. She received multiple electroshock therapy. She died of metastatic breast cancer at 65.

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The mother, a high school graduate, has histoplasmosis of the eye. There is no history of mental disturbance in her family.

The patient has two sisters and a brother. The older sister, age 20, is a high school graduate and has no known medical problems.

A sister, 16 years old, was diagnosed as PKU at age three and was never treated. Her current serum phenylalanine was 32.6 mg%, serum tyrosine 0.9 mg%. Urinary metabolites revealed phenylacetic acid 1.6 μm/cc, o-OH phenylacetic acid 0.6 μm/cc, phenyllactic acid traces; phenylpyruvic acid 12 μm/cc. Wechsler Intelligence Scale IQ estimated at 35-40 at 16. She is currently in a special school. EEG recording revealed mild abnormalities.

A brother, 12 years old, is in the seventh grade. He has difficulty with mathematics and basic number concepts and requires special tutoring but is not phenylketonuric.

Physical Examination

On admission, the patient weighed 107 kg, was 194 cm in height and head circumference was 60 cm. With the exception of eczema, the physical examination was within normal limits.

Examination revealed a restless and agitated person with slight press of speech who occasionally paused to look at the ceiling and speak in phrases such as, "Get out of here!" He admitted to frequent hallucinations and stated that there was a group of people, with specific names and appearances, who were trying to "capture his mind," but that he was resisting successfully. He denied any visual hallucinations. He has had delusions of persecution and control by others. He was cooperative with the examiner at times, but on other occasions he acted as though the examiner was not present. He was oriented with normal immediate recall but had difficulty with serial subtraction and simple calculations.

Psychological Testing

His Minnesota Multiphasic Personality Inventory (MMPI) was suggestive of a thought disorder of psychotic type and degree. His full scale IQ by Wechsler Adult Scale was 78, with a verbal quotient IQ of 89, memory DQ of 68 and perceptual organization of 92. Porteus Maze test quotient was 61. Bender Gestalt reproductions were unremarkable and Bender recall was low average, three of nine, showing some perseveration from previous test material. Bilateral tremor of the hands was noted on all tests. Overall, the impression was that of "low average intelligence with no clear evidence of cerebral dysfunction of other than functional origin." During his hospitalization, he was given daily Nosie observational examinations. Wittenborn psychiatric scales were done weekly. Videotaped interviews were evaluated on the basis of the Inpatient Multi-Dimensional Psychiatric Scale.

The patient spent considerable daytime hours in bed, engaging almost constantly in talk with himself. During these periods, he had arguments with voices over his appearance and intelligence. His clinical picture suggested a classic hebephrenic schizophrenia. EEG records revealed mild abnormality due to bilateral, irregular, intermittent low voltage, slow activity in the theta range. Extensive laboratory investigations, including blood studies, kidney function, electrolytes, serology, HVA and 5HIAA spinal fluid analysis, and chromosome studies by mid-metaphase and Giemsa banding technique, were within normal ranges.

Serum phenylalanine, before and after discontinuation of the diet, varied from 19.9 to 34.2 mg%, serum tyrosine was 1.4 mg%. Urinary metabolites, during regular diet, contained 473 μm/cc phenylacetic acid, 289 μm/cc of o-OH phenylacetic acid, 633 μm/cc phenylpyruvic acid and 201 μm/cc phenyllactic acid. His weight before dietary restriction was 107.8 kg. Daily food intake, prior to dietary restriction, varied from 2550-3100 calories with approximately 110-135 gm protein.

A diet low in phenylalanine was initiated for six weeks with an original phenylalanine allowance of 30 mg/kg/day but this was reduced to 20 mg/kg/day. His serum phenylalanine on the diet was 12.3 mg%, with a great reduction of phenylketones in the urine, a trace of o-OH phenylacetic acid and no phenyllactic acid. Although he lost 9 kg, he showed no basic changes in his daily behavior, no decrease of hallucinations, and no changes on psychiatric scales, MMPI or EEG recordings. Discontinuing the diet and varying different drugs and doses failed to control his hallucinations.

Discussion

According to our knowledge, this is the first PKU patient who developed schizophrenia and was prescribed a diet low in phenylalanine in an attempt to influence his symptoms. Our patient and the subjects described by Perry et al.[4] suggest a relationship between PKU and schizophrenia. The following factors and relationship of the two diseases can be considered: (1) emotional stress, (2) biochemical factors, (3) genetic factors, and (4) coincidence.

Emotional Stress

Stressful situations may provoke signs of schizophrenia in a PKU patient of subnormal intelligence. Physical, social and psychological stresses have at times been blamed for initiating schizophrenic behavior in individuals having genetic disorders with specific brain dysfunction.[6] Employment of the patient, away from the protection of the school and home environment, disturbed him: he displayed lack of self-confidence and healthy self-image, dependence on concrete directions and supervision, a strong tendency to try to please people, especially his superiors, and resented people calling him names and making fun of him because they thought he was retarded. His schizophrenic symptoms may have been triggered by these circumstances and his inability to cope with these stresses may be the result of mental dysfunction. Repeated failure to adjust can result in poor self-image and, possibly, schizophrenic reactions.

Biochemical Factors

There are several biochemical influences which could account for the symptoms of this patient. Phenylethylamine, a biogenic amine similar in properties to but less potent than amphetamine, a metabolite of phenylalanine, has been identified in the urine of PKUs.[7] Metabolites of catecholamines are reduced in PKU, suggesting either decreased synthesis or turnover of the transmitters.[8-10] The catecholamine hypothesis of affective disorders[11] is consistent with the depressed or "morose" personalities of many PKUs, and might be the basis of schizophrenic symptoms. Disorders of tryptophan metabolism have been described in PKU.[12] Decreased blood content of serotonin and reduced excretion of 5-hydroxyindolacetic acid, an excretory product of serotonin, have been reported; like catecholamines, serotonin has been implicated in depressive disorders.[13] Decreased serotonin in both schizophrenia and PKU has been observed.[14] Tryptophan, via the pyrrolase reaction, leads into the synthesis of nicotinic acid. Metabolites of phenylalanine have been shown to partially inhibit this reaction.[15] Symptoms of psychosis as seen in pellagrins could be the result of *in situ* pyrrolase inhibition in PKUs. Furthermore, transport of tyrosine in the brain is inhibited by excess phenylalanine or tryptophan;[16] thus, brain nutrition may be disturbed and could lead to a toxic brain syndrome in PKU. A more speculative cause of mental disorders is the effects of these chemical influences on the developing brain. Permanent changes in brain function could result from even short-term chemical derangement during a critical period of growth.[17] These, or other as yet unknown neurochemical derangements, might be the basis of schizophrenia in PKU.

Genetic Factors

Genetic and clinical data suggest that an autosomal, recessive gene is responsible for PKU.[18,19] In schizophrenia, a genetic variation is regarded as a hypothesis; yet, a single autosomal gene is considered primarily responsible for the disorder, manifested in all homozygotes and in approximately one-fourth of heterozygotes.[20] It has already been suggested that heterozygotic carriers of PKU may be more liable to depressive illnesses. Increased incidences of paranoid illnesses in later life in the unaffected relatives of PKUs have been reported.[18] Munro found twice the expected rate of psychosis among the relatives of PKUs than in control families.[21] An increased incidence of psychosis, suicide and alcoholism was noted[22,23] among family members of a limited number of reported phenylketonuric families. A high incidence of electroencephalographic abnormalities was found among parents and siblings of PKUs.[24] However, other studies have failed to show a greater incidence of psychosis among relatives of phenylketonuric patients than comparative relatives of other mental defectives.[25,26]

A significantly higher fasting serum phenylalanine level was found in a group of schizophrenics than normal subjects on the same diet.[27] Although the relationship between heterozygosity of PKU and psychosis is obscure and limited, the cases of Perry et al.[4] and ours suggest a possible linkage between the homozygous PKU and schizophrenia. The current symptomatology of the patient could be explained by the acceptance of the biochemical predisposition, although he did not respond favorably to dietary restriction. However, the symptoms may be the result of mental dysfunction secondary to an existing anatomic or chemical defect not related to current levels of phenylalanine or its metabolites.

There are three genetic possibilities for the grandmother: (1) She was phenylketonuric and her problems were due to underlying biochemical changes. How-

TABLE

Patients with Phenylketonuria and Schizophrenia

Source	Age at onset of symptoms (yrs)	Sex	Serum phenylalanine (mg%)	IQ	PKU No.	Siblings IQ (sex)	Schizophrenia in family	Other	Comments
Perry, et al.[4]	28	F	14-17	83	2	106 (F)	not mentioned	of 3 PKU mothers, 9 children mentally retarded & 2 aborted	diagnosis of PKU made after schizophrenia treated by electric shock therapy mentioned only in paper — no details
	28	F	17	90-95			not mentioned		
	35	F		68					
	47	M		ment. def.					
Pitt[32]	adolescent			imbecile					among 53 cases of PKU schizophrenia no details to schizophrenia are mentioned
	49								
Bjornsen[33]	11	F	32	65-70	1	30 (F)	mother psychotic, received electric shock therapy father mentally ill		
Present case	22	M	19-32	85	1	30 (F)	grandmother		

ever, the statistical possibilities are against this; among her four children, none have had the stigmata of maternal PKU (mental retardation,[28] growth retardation,[29] and malformations[30,31]). (2) The grandmother was heterozygous for PKU and, as such, had a greater likelihood of psychosis. (3) The grandmother was not even heterozygous and her schizophrenia was a separate disorder.

Coincidence

The number of reported patients are too few (Table) to justify any statistical conclusions although in our patient's family and in the cases of Perry et al.[4] 50% of the PKU patients developed schizophrenia.

Recognition of a few patients may be due to the fact that severely retarded PKU patients prior to the era of dietary restriction simply were not observed manifesting the symptoms of schizophrenia. Perry mentions two additional PKU patients with schizophrenia but does not describe them in detail.[4] Two additional schizophrenics among 58 institutionalized PKU patients were reported,[32] again without further detail, and one 11-year-old retarded PKU child had some schizophrenic symptoms.[33] In spite of the limited number of cases, there is suggestive evidence among the relatives of PKUs, the behavior patterns of retarded PKUs, the biochemical similarities and finally, between the homozygous PKU patient and schizophrenia, to conclude that the two have more than a coincidental relationship. Therefore, similar cases with less obvious signs of schizophrenia most likely occur among the treated as well as the untreated phenylketonuric with normal or borderline intelligence and should be looked for with diligence.

The exact link between phenylketonuria and schizophrenia is not established. A common biochemical pathway is established and a genetic link between the two disorders is suggested. But this is only theoretical, since neither PKU nor schizophrenia genes have been localized to any particular chromosome by current methods of detection.

Perry's patients, like ours, were not treated early.[4] Perhaps patients treated early will escape such problems. Similar case(s) may be overlooked. Although dietary restriction in our patient had no effect, this is not proof that the disorders are unrelated. The damage may have already been done and is irreversible, or PKU may well be more complex than presently suspected. The fact that we can control the serum concentration of phenylalanine does not mean we totally understand or have effectively controlled the disease and its complications. We must concern ourselves not only with the detection and treatment of PKU, but also encourage genetic counseling of prospective parents. The management of PKU can no longer be restricted to pediatrics. In cases where there are signs of schizophrenia, PKU should be considered among the differential diagnoses.

Acknowledgment

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MMA Annual Luncheon
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"Why Don't They Tell The Truth About Old Age?", George Sheehan, M.D., Redbank, New Jersey — cardiologist, Best-selling author, columnist, marathon runner.

Post-Operative Headache

A Manageable Complication

JOHN B. BRAINARD, M.D.*

In patients with a history of migraine or vascular headaches, natiuresis was induced by furosemide when headache developed after a variety of surgical procedures. The headaches were rapidly terminated in all cases.

MANY PATIENTS HAVE transient headaches after surgery. While this is not a life-threatening complication, it adds to the discomfort of the patient and may indicate electrolyte imbalance. There is recent evidence that sodium chloride loading will trigger migraine or vascular headache.[2] This investigation was undertaken to determine if manipulation of sodium chloride administration and excretion in surgical patients could terminate post-operative headache.

Material and Method

Patients with a history of frequent vascular headaches were observed for the occurrence of headache after a variety of general surgical procedures. Intravenous normal saline or dextrose 5% in lactated Ringers solution was administered routinely after surgery at 125 cc/hour until headache occurred.

As soon as the patient informed the nursing staff of

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*St. Paul, Minnesota.

TABLE 1.

Effect of Furosemide on Post-Operative Headache

Case	Surgery	IV Fluids	Treatment	Results	Serum Na+
1	Common bile duct exploration	D_5S 125 cc/hr	DC D_5S Furosemide 20 mg IV	Headache ceased in ½ hr	Pre-op 140 mEq/L Headache 145 mEq/L Post-headache 141 mEq/L
2	Appendectomy Excision of ovarian cyst	D_5W in LR 125 cc/hr	DC D_5W in LR Furosemide 40 mg IV	Headache ceased in 1 hr	Headache 136 mEq/L
3	Thyroidectomy	D_5S 125 cc/hr	DC D_5S Furosemide 20 mg IV	Headache relieved, recurred after high Na+ lunch	Not measured
4	Cholecystectomy	3,800 cc D_5S in 24 hr	DC D_5S Furosemide 20 mg IV	Headache relieved in 20 min	Not measured
5	Vagotomy & Antrectomy	D_5W in LR 125 cc/hr	DC D_5W in LR Furosemide 40 mg IV	Headache relieved in 30 min	Pre-op 137 mEq/L Headache 145 mEq/L 3 d PO 137 mEq/L
6	Vagotomy, pyloroplasty Nissen fundoplication	D_5S 125 cc/hr	DC D_5S Furosemide 40 mg IV	Headache ceased in 30 min	Pre-op 137 mEq/L Headache 140 mEq/L Post-headache 138 mEq/L
7	Modified radical mastectomy	D_5S 125 cc/hr	Furosemide 40 mg IV Wigraine 1 tab	Headache relieved in 2 hr	Not measured
8	Excision intraluminal duodenal diverticulum	D_5W in LR 125 cc/hr	DC D_5W in LR Furosemide 20 mg IV	Headache relieved in 40 min	Headache 141 mEq/L Post-headache 135 mEq/L

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CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components. Do not use in the eyes or in the external ear canal if the eardrum is perforated.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne i mind that the skin is more liable to becom sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failu to heal. During long-term use of neomycin-containin products, periodic examination for such signs is advisable and the patient should be told to discontinu the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoide for that patient thereafter.

PRECAUTIONS: As with other antibacterial prepar tions, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

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Complete literature available on request from Professional Services Dept. PML.

the presence of a headache, the intravenous infusion was changed to dextrose 5% in water and continued at 125 cc/hour. At the same time, the patient was given 20 or 40 mg of furosemide intravenously.

Discussion

In every case, the headache was terminated by administration of furosemide and discontinuing the saline infusion (Table 1). This was accompanied by a profound diuresis and excretion of sodium well above normal values (Table 2).

There is recent evidence from computerized axial tomography brain scans[3] that reversible cerebral edema occurs in migraine headaches. The stress of surgery is known[1] to cause release of adrenal hormones and consequent retention of sodium and water. There is also clinical evidence[2] that sodium loading will precipitate migraine in susceptible patients. The relief of headache by furosemide induced natiuresis appears to demonstrate a cause and effect relationship between sodium retention and post-operative headache.

Even though it is known that sodium retention occurs after surgery, it is almost universal practice to give saline infusions during and after operative procedures to maintain normal urine volume by osmotic diuresis. The appearance of headache may be a good indicator that sodium overloading has occurred and that the intravenous infusion should be changed to a non-electrolyte solution, such as dextrose 5% in water.

TABLE 2.

Urinary Excretion after Furosemide

Case	Urine Output	Urine Na+	Urine Sp Gr
1	2,230 cc/24 hr	—	—
2	2,250 cc/24 hr	—	—
3	2,825 cc/24 hr	—	—
4	3,840 cc/24 hr	768 mEq/24 hr	1.009
5	2,650 cc/24 hr	363 mEq/24 hr	1.009
6	3,550 cc/24 hr	238 mEq/24 hr	1.025
7	4,100 cc/24 hr	353 mEq/24 hr	1.007
8	2,925 cc/24 hr	—	—

Normal (43-217 mEq/24 hr)

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The new and excellent film ALCOHOL, PILLS AND RECOVERY, produced under the direction of Doctor Joseph A. Pursch, Chief of the Navy Alcohol Rehabilitation Service at the Naval Regional Medical Center in Long Beach, California, will be shown and discussed by Doctor Pursch and a panel of Minnesota physicians involved in chemical dependency programs. General group discussion will be encouraged. The objective of this course is to deepen our understanding of the problems of chemical dependency, particularly alcoholism, and to improve our ability to help patients with such problems.

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Rheumatology Corner

Planning A Treatment Program for the Patient with Rheumatoid Arthritis

JOHN G. MAYNE, M.D.*

THE OUTLOOK FOR patients with rheumatoid arthritis is a lot better than most patients or physicians believe. With currently available treatment, we can expect definite clinical improvement in 75 per cent of patients with arthritis of less than one year, and we can expect complete remission in 15 to 20 per cent. Current treatments will not cure or even definitely arrest rheumatoid arthritis in all patients. What we hope for when the disease does not spontaneously remit is to suppress the active disease process, to relieve symptoms, and to restore function to damaged joints, muscles, and tendons.

The active systemic disease can be suppressed at least partially in many patients by a simple basic program of extra rest, planned and supervised physical therapy, and simple analgesic or anti-inflammatory medications (especially salicylates). Treatment programs using drugs of greater risk, may be necessary in some patients. Local treatment measures such as intra-articular injection of steroids are useful especially early in the disease in some patients. If the local joint reaction is more persistent or has already produced damage, surgery may be necessary to relieve pain and improve function.

Rest is ''number one'' in importance in this basic program. Early in the illness, a patient may gain most by three to four weeks of total bedrest (preferably in a hospital if it is economically and psychologically possible). Even when the disease seems controlled, extra rest is important. A minimum of ten hours of bedrest at night and one to two hours midday should be recommended. The patient does not have to sleep during the rest period, but mild activity — even sedentary — is not an adequate substitute. Always, it is important for the patient with rheumatoid arthritis to avoid excessive fatigue.

But bedrest alone is not adequate. Rest without therapeutic exercise may actually be responsible for flexion contractures or muscle atrophy. The patient needs a daily program of physical therapy including heat and exercise appropriate to his clinical symptom. Heat, whether moist or dry, is useful in relaxing tense, painful muscles. It should be followed by an exercise program individually designed to maintain as normal a range of joint motion as possible without undue stress on involved joints. It also discourages muscle disuse and atrophy. Yet, the patient should protect and not ''overuse'' involved joints.

Systemic anti-rheumatic agents may be considered in one of three categories: analgesic and antipyretics such as salicylates, phenylbutazone, indomethacin, ibuprofen, fenoprofen, naproxen, tolmetin, and the recently marketed sulindac, agents known to suppress the active disease process such as gold salts, antimalarials and Penicillamine, and the immunosuppressive drugs including azathioprine, chlorambucil, methotrexate, and cyclophosphomide. Low dose steroids (less than 10 mg a day of Prednisone) acts somewhat like milder anti-inflammatory analgesics; high dose steroids act more like immuno-suppressive medications.

When systemic rheumatoid disease is not adequately controlled by the basic program and the medications just discussed, and when persisting synovitis threatens permanent joint damage, systemic measures probably should be supplemented with local injection of a steroid preparation into inflammed areas whether intrasynovial, bursal, or tenosynovial. There is usually some systemic effect from the intra-articular use of steroids.

When the basic measures, including drugs, and local injections of steroids are not adequate to control the individual joint reactions, surgical procedures should be considered. Synovectomy is the treatment of choice if the joint has not been damaged extensively, whereas arthroplasty or arthrodesis should be considered if the joint already has undergone substantial and disabling damage.

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*Associate Professor of Medicine, Mayo Medical School, Rochester, Minnesota.

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Editorials

Mononuclear Infiltrates in the Myocardium

Clinical medicine is a fledgling science. Despite the recent technological explosion of CTs, SMAs, and RIAs, we still struggle with inexact syndromes and symptom complexes without scientific explanations. Coughs, sore throats, and pains are frequently blamed on "viruses," and the patient's cure left to antibodies, chicken soup, or divine intervention — and most do get better. Bandt, et. al.* in this issue remind us that another common syndrome, sudden death, can indeed be caused by viruses and that scientific documentation must frequently await that final diagnostician, the pathologist. They present three cases of sudden death in the pediatric age group where pathological exam revealed mononuclear infiltrates in the myocardium, presumably from a viral infection.

Although other etiologies such as toxins or allergens can produce similar pathological changes and the viral causation must remain speculative, these cases highlight the inadequacy of our clinical descriptions and the difficulty in diagnosing viral diseases in general and myocarditis specifically. Despite its well-publicized link with coronary artery disease, sudden death can result from multiple pathological etiologies. Presumably the mechanisms common to sudden death from coronary disease, and myocarditis or unknown causes, are conduction disturbances or tachyarrhythmias. With further technological advances, the classification of "idiopathic" sudden death will presumably shrink.

Myocarditis has multiple faces and perhaps occurs more frequently than clinically recognized. In addition to sudden death, congestive heart failure, supraventricular tachycardias, and A-V block can be caused by myocarditis. Myocarditis can mimic myocardial infarction, pericardial effusion, or cardiomyopathy of other etiologies. Because therapy and prognosis obviously differ, establishing myocarditis as the diagnosis is important. As pointed out by Bandt, et. al. myocarditis is a difficult diagnosis to make. Technology does offer some promise in making these distinctions. Echocardiography can diagnose pericardial effusion non-invasively and accurately. Although it doesn't pinpoint etiologies, echo can assess ventricular dimensions and function. Myocardial biopsy is a potentially useful tool for pre-mortem pathological confirmation. Recent rapid viral antibody determinations which can establish etiology will become more relevant as antiviral chemotherapy develops.

So there is hope that we will move out of our benighted practice of calling all colds "viruses" and all sudden death coronary artery disease. As technology progresses, the true incidence of myocarditis may become appreciated, and perhaps then clinical medicine will earn the title science.

Charles R. Meyer, M.D.
Minneapolis, Minnesota

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*See page 234.

Cholelithiasis in a Child without Hemolytic Anemia

The only rule in medicine that seems to have no exception is that there is no Always and no Never. I would agree that the radiologist should be aware that Cholelithiasis and Cholecystitis may occur without evidence of Spherocytosis or Sickle Cell disease. However, Arey[1] after an experience of thirty years in a busy Children's Hospital reports the occurrence of stones without the above conditions at autopsy to be extremely rare. Kaye and Holtzapple[2] speculate that someday the detection of individuals susceptible to Cholelithiasis will be possible and the early use of Chenodeoxycholic acid or similar agents will diminish the importance of Cholelithiasis as a gastro-intestinal disease.

Stuart Lane Arey, M.D.
Minneapolis, Minnesota

See page 223.

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1. Arey, James B. Personal Communication.
2. Kaye, Robert and Holtzapple, Phillip, in Nelson Textbook of Pediatrics 10th Edition W.B. Saunders 1975, Page 899

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Micropolycystic Liver and Gluten Sensitivity — So What?

> *Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rare forms of disease.*
>
> *William Harvey*[1]

IN THIS ISSUE, a case report is presented of two not very common entities, micropolycystic liver disease and gluten enteropathy, existing together.* The authors assume this coexistence to be coincidental; they do not speculate on a possible connection to the patient's death from acute myocardial infarction. One thus might question the justification of this report. Does the Journal need this type of paper to fill its pages? Could there be already too many reports of incidental findings?[2] But medical history has many examples of case reports advancing our knowledge substantially, and occasionally a well-described observation, often made in one or two patients, became the spark igniting the entire field.[3]

We must be inquisitive concerning possible connections between problems which at first glance seem unrelated to each other, yet they occur in the same patient. I feel strongly that the term "coincidence" may be nothing but the admission of our ignorance, leading to complacency. It may well be that reports such as this shed new light on old problems. What if the patient's sick liver deprived his cardiovascular system from protective factors, viz. HDL, a lipoprotein said to be beneficial for the cardiovascular system (measurements of VLDL or HDL are not given here). One might also speculate that his diabetes mellitus may have been related to his liver disease, as the liver plays a definite role in glucose metabolism. The gluten enteropathy could certainly have aggravated or triggered existing problems, if by no other means than possible electrolyte abnormalities (he frequently had diarrhea).

Thus we should continue to look aside the beaten path as Harvey tells us so beautifully in the above quotation. Who knows, one day we may no longer have to belabor coincidence in a case like this.

C. A. Pierach, M.D.
Minneapolis, Minnesota

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*See page 231.

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1. The works of William Harvey, translated from the Latin by Robert Willis. Letter to John Vlackveld, Harlem, 1657. London, Sydenham Society, p. 616, 1847.
2. Rubin, A: An unwritten "Case Report" (Letter to the Editor). N Engl J Med 300:96, 1979.
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Cholestasis of Pregnancy

CHOLESTASIS OF pregnancy (recurrent jaundice of pregnancy, icterus gravidarum, obstetric hepatosis, cholestatic hepatosis) is an uncommon, yet benign condition usually occurring during the third trimester and characterized by pruritis and/or icterus. At times, the pruritis may be quite discomforting to the patient. Mattson and Olson* report a patient in late pregnancy with pruritis and questionable jaundice but resulting in no sequelae.

This condition is characterized by abnormal liver function studies which indicate impaired biliary excretion and pathologically by centrilobular bile staining of the liver. Pruritis is due to the increased deposition of bile acids in the skin. When treatment is required, the patient usually will respond to the administration of cholestyramine which is an anion-exchange resin that absorbs and combines with bile acids in the intestines. This allows excretion of the bile acids into the bowel and blocks its return to the liver via the enterohepatic circulation.

Cholestasis of pregnancy usually disappears after delivery, but often will recur during subsequent pregnancies or during subsequent use of highly estrogenic birth control pills. As described in the article by Mattson and Olson, the fetus and infant may be at risk.

William C. Meyer, M.D.
Minneapolis, Minnesota

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*See page 261.

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Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage

WIDE APPLICATION of cardiopulmonary resuscitation (CPR) has undoubtedly resulted in prevention of death in a great many patients. In Minnesota, we are particularly indebted to the leadership of Dr. Brian C. Campion and the support of the Minnesota Division of the American Heart Association for increased awareness, training and general dissemination of this body of knowledge. Although CPR generally is considered a safe and simple technique, being widely employed by trained laymen, this report by Dr. Kenton Bodily* and associates brings attention to the fact that it is not innocuous and may be associated with serious or possibly fatal complications. Indeed, a scan of the literature indicates as many as *fifty different* complications, some of which may be fatal. For obvious reasons it is appropriate that these same training methods previously instituted be utilized to bring increased awareness of these problems to both the medical profession and laymen as well.

It would appear that the use of mechanical compression devices for CPR should be carefully limited.

Joseph C. Kiser, M.D.
Minneapolis, Minnesota

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*See page 225.

Book Reviews

ULCERS. by M. Michael Eisenberg. pp 240. Octavo Random House, N.Y. 1978-$8.95.

Even if a private physician could afford to spend five or six hours discussing with a long suffering patient every detail of his peptic ulcerous problem; its causes, variations, complications, therapy medical and surgical, prognosis, etc., etc., there would remain a need for a book such as this. In terms of informed consent so fashionable these days, here is an easy way for the physician to inform his patients with peptic ulcer of their problem: Just read this book. It can be done in five or six hours and if you are incautious enough to start reading in the evening, I warn you, you will probably pass your bedtime with the book in your hands because like a good novel it is hard to put down. This surgeon, Eisenberg, writes English that is easy to read. He is writing for the patient; and I, an unulcerated physician, found his book utterly fascinating.

The book is profusely illustrated with brief case studies, but no photographs and a few diagrams. One aspect of peptic ulcer he did not cover sufficiently is "Ulcer as a Crutch" and in the style of Eisenberg I will present a case:

> Minneapolis Minnesota 1937
>
> Hymie is a 52-year-old cooper for the D — Barrel works. He has known of a duodenal ulcer for the past 15 years. At first he would miss about a week's work spring and fall with belly pain, but gradually his incapacity extended so that for the past three years he had been out of a job. To make ends meet the wife went out on day work five days a week and Hymie, between milk on the hour and antacid on the half hour, took over the housework, cleaning, bedmaking, cooking, everything — until he came to me as a patient. I diagnosed an intractable ulcer and recommended surgery (Hemigastrectomy?) which proved curative and Hymie was back at the barrel factory in three months. I never saw him again, but the depth of his disapproval of my course of therapy can be gauged by the fact that he didn't pay his bill. I had totally disrupted a happy compromise he had reached with his disease and forced him back to (ugh) work! Three years after the medical service, one day I received a check in the mail for $5.00; a token, I suppose, that I was forgiven and he was willing to accept his inevitable cure.

Now for some advice to my good friend, Mike, for the next edition. Please tell Random House when you cite a number for a figure, one should find a corresponding number on a figure. And don't forget when you publish the next jacket blurb to include the fact that your first position when you came to Minnesota in 1968 was Director of Surgical Education at Mount Sinai Hospital, Minneapolis.

Reuben Berman, M.D.
Editor Emeritus

SCABIES AND PEDICULOSIS. Edited by Milton Orkin, Howard Maibach, Laurence Parish, and Robert Schwartzman, J.P. Lippincott Company, Philadelphia and Toronto, 203 pages.

In May 1976, an International Conference on Scabies and Pediculosis was held in Minneapolis. Much of the material from that conference is included in this book. This well-bound paperbound book contains 31 papers. The authors are authorities from academic centers around the world, and their papers are well-illustrated, with good quality line-drawings, numerous tables and charts, and excellent color plates to illustrate clinical manifestations of scabies and pediculosis.

Scabies has reached epidemic proportions around the world. It is seen in 2 to 4 percent of patients in dermatologists' offices and should be in the differential diagnosis of pruritic dermatoses. Two of this book's editors, Milton Orkin of Minneapolis and Howard Maibach of San Francisco, followed this book with an excellent article on scabies in the March 2, 1978 issue of the *New England Journal of Medicine*. ("This Scabies Pandemic", *N Engl J Med*, 29: 497-498). I commend that article and this book, even if your interest in dermatology is only skin-deep and even though you find extra reading a mite of a pest.

Richard C. Reece, M.D.
Editor-in-Chief

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Letter to the Editor

The Barium Enema: Is It Alive?

WE HAVE HAD inquiries from the private sector of radiology as to whether the barium enema examination was still alive at the University of Minnesota Hospitals. We can report the barium enema is still very much alive and well at UMH.

We concur with the recommendations pertaining to Radiology from the conference on the screening and early detection of colorectal cancer sponsored by the Division of Cancer Control and Rehabilitation of the National Cancer Institute, June 26-28, 1978. "The appropriate national professional organizations should educate the radiological, medical and surgical communities regarding the importance of air contrast study in addition to the standard barium enema examination in the roentgenographic examination of the patient suspected of having a neoplasm or small polypoid lesion of the colon. Physicians should be encouraged to assume responsibility for adequate cleansing of the colon prior to the barium enema examination. The risk and expense of this roentgenographic examination are not justified in poorly prepared patients".[11]

"The clean colon" is essential to the radiologist regardless of what type radiologic examination is performed. Seventy-five percent of carcinomas missed on x-ray examination are the result of their being mistaken for or obscured by fecal material.[1] The greatest fallibility of the radiologist has been that of not demanding as clean a colon as the colonoscopist. Painfully we have come to accept the conclusion of Miller,[8] "the cleansing enema should be the responsibility of the radiologist"; "it is literally a life-saving measure". We are now giving cleansing enemas in the radiologic department at the UMH.

We do not deny that colonoscopy is a sensitive method for colon examination; nevertheless the colonoscopists miss lesions also.[3,10] Comparative studies have shown that roentgen examination and colonoscopy may be comparable for demonstrating lesions 1.0 cm or larger in size.[4,12,14] Williams et al.[14] state "nonetheless, to realize the potential advantage of barium enema studies over colonoscopy as a potential screening procedure it is only necessary to watch the relative technical difficulty, slowness and discomfort often involved in total colonoscopy and to compare the ease and speed with which a radiologist can fill the colon with barium and air". According to Marks,[7] "colonoscopic examination is far too costly to be used as either a screening procedure or routine method of examination".

Currently our recommendations for each type of examination are as follows:

A. Indications for primary double contrast enema
   1. Rectal bleeding or positive hemoccult
   2. History of polyp
   3. Family history of carcinoma of colon or polyposis
   4. Looking for carcinoma (e. g. change in bowel habits, weight loss, unexplained anemia, unknown primary)
   5. Previous carcinoma of the colon
   6. Obesity (because of inadequacy of compression necessary for conventional barium enema technique)

B. Indications for Conventional Barium Enema
   1. Abdominal mass of any cause
   2. Known or suspected pelvic metastases especially from cervix or endometrial carcinoma
   3. Pre- or postradiation
   4. Endometriosis and other GYN related conditions
   5. Suspected obstruction of the colon
   6. Desirability of retrograde examination of terminal ileum (with double contrast enema an attempt is made to avoid reflux into terminal ileum)

C. Indications for Water Soluble Contrast Enemas
   Should be reserved for suspected perforations[6] such as:
   1. diverticulitis
   2. perforated carcinoma
   3. leaking anastomosis
   4. abdominal stab wounds communicating with the colon

In inflammatory bowel disease mucosal lesions can be better seen with double contrast enemas,[2] but the conventional barium enema may be preferable to see the extent of the disease or examine the terminal ileum.[9] In toxic megacolon both are contraindicated.

Our experience and review of the literature leads us to conclude: (1) Most radiologists are now in agreement that the double contrast examination, either primary or secondary, has sigificant advantage over the single contrast barium enema for detection of polyps and for screening the patient at high-risk for colon cancer.[5,11-14] (2) The double contrast barium enema and colonoscopy are complimentary.[12,15] (3) Their combined accuracy exceeds that of either technique alone.[12,15] (4) Each has its advantages and limitations.[7,10,14]

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Mathis P. Frick, M.D.*
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Minneapolis, Minnesota

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*Assistant Professor of Radiology, Assistant Professor of Radiology, Professor of Radiology, Professor and Chairman of Radiology, University of Minnesota Medical School, Twin Cities.

See references on page 277.

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Review

Cholestasis of Pregnancy

DONALD S. MATTSON, M.D.,* and GREGORY M. OLSON, M.D.†

A case of cholestasis of pregnancy is reported, an uncommon, but not rare disorder, usually marked by moderate to severe pruritis in late pregnancy, mild jaundice and mild elevation of 'liver enzymes' and blood lipids. A genetic error of steroid metabolism with impaired bile acid hepatic transport appears etiologic. The fetus may be endangered. Bile salt binding resins provide adequate therapy. Oral contraceptive therapy may be complicated by similar findings.

CHOLESTASIS OF PREGNANCY, though recognized as early as 1883, and, in spite of being a relatively common disorder in certain areas of the world, was not cohesively analyzed and described until 1955 when Thorling[36] described thirty-eight patients with jaundice late in pregnancy. Since then numerous reports have appeared describing the same syndrome in pregnant patients and more recently in users of oral contraceptives.

Case Report

This 20-year-old girl was seen in consultation complaining of itching on the palms and soles, with dark urine for approximately one month. She had had scleral icterus, but no severe jaundice. Her referring physician stated that her SGOT was mildly elevated. She gave no history of known exposure to jaundiced persons or any medications except multivitamins and ampicillin, which she had taken two months previously. There was no evidence of toxic exposure except a "pest strip" hung in the kitchen all summer. There was no history of abdominal surgery. She had noted some pressure-like discomfort under the right rib cage, but no severe pain, or food dyscrasias. At the time of examination she was pregnant, two weeks away from her expected date of confinement. During her pregnancy there had been no unusual vomiting. No personal or family history of any hematological disorder was given, nor had there been during pregnancy any elevation of her blood pressure. She gave no history of excessive alcohol intake. This was her second pregnancy, the first pregnancy and delivery being normal.

Physical examination was completely normal, except for the enlarged uterus. There was no scleral icterus or hepatosplenomegaly. No rash was noted on the skin.

Laboratory Studies

Hemoglobin 13.3 grams%, hematocrit 37.5 vol%, WBC 12,100 per cubic millimeter, differential N 70, L 29, E 1. Reticulocyte count 1.8%. A peripheral blood smear was normal. Urinalysis: specific gravity 1.017, albumin trace, sugar 0, bile small amount; microscopic, WBC 1-3 per hpf, occasional RBCs, many bacteria and epithelial casts. A blood biochemical profile was normal, except for an alkaline phosphatase at 471 u/l (normal 80-225), SGOT 25 u/l (normal up to 17), cholesterol 367 milligrams percent, triglycerides 461 milligrams percent. Serum bilirubin was 0.4 mg%. LDH, serum proteins were normal. Calcium was 8.8 mg%. Phosphorous was 3.7 mg%. Blood type was 0, Rh positive. A chest Xray was normal. Gallbladder Xrays were not done at this time.

Diagnosis: 1. Probable idiopathic cholestasis of pregnancy.
2. Rule out early biliary cirrhosis, drug toxicity.

She was offered cholestyramine as therapy for her itching, but she did not feel it was severe enough to warrant any therapy so no treatment of any kind was given. She delivered her baby two weeks later and was relieved of all symptoms within one week. The blood biochemical profile was repeated two weeks later, the SGOT having fallen to 11 u/l, alkaline phosphatase to 216 u/l, cholesterol to 214 mg% and triglycerides to 146 mg%. Serum bilirubin was 0.6 mg%.

Incidence

Cholestasis of pregnancy is not a common problem, the incidence varying from 0.004% to 2.4% depending on the criteria used for its definition.[4,29,31] Svanborg & Ohlsson[34] reported an incidence of 0.2% of total deliveries in one of the Scandinavian Countries where the incidence would appear to be highest, and Cahill[4] described four cases seen in a total of 110,378 pregnancies delivered over 28 years in New York.

Clinical Presentation

Cholestasis of pregnancy is usually marked by mild symptoms.[6] Pruritus, which may be severe, may or may not be followed by jaundice which is generally mild, appearing in an otherwise normal gestation. Patients may experience anorexia, nausea, occasional vomiting, and they may note some right upper quadrant pain which may be associated with some liver enlargement. The spleen is not felt. Johnson et al.[14] reported a higher incidence of emesis, and food and drug idiosyncrasy in the patients they studied.

More often than not the symptoms appear in the last trimester of pregnancy,[6,10] though Thorling[36] found that in his original series of patients, jaundice appeared in the first trimester of pregnancy in eight of the

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*Willmar, Minnesota.
†Litchfield, Minnesota.
See editorial, page 255.

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thirty-eight patients, and Drill[6] noted considerable variation in the appearance of these symptoms during respective pregnancies. Jaundice or pruritus may occur in the first pregnancy, or may not appear until the third or fourth pregnancy. Once they appear, the symptoms frequently recur in subsequent pregnancies, though not always. One may note jaundice in one pregnancy, and only pruritus in the next, and cases have been reported with jaundice in several successive pregnancies followed by no symptoms at all in the next gestation. Recurrence is reported to occur in about 50% of these patients.[9,10]

Course and Prognosis

Furhoff and Hellstrom[11] and others[5,6,14,16,34,36] observed that the course was a benign one for the mother, both in the short term and after long term follow-up, except for a report of BSP retention in eight of thirty eight patients followed by Furhoff and Hellstrom over a long period of time, and possibly gallstones which may appear years later.[11] Following delivery, jaundice disappears in one to four weeks and there is rapid and complete resolution of both symptoms and laboratory evidence of disease.[6,10] If the patient has had only pruritus without jaundice, the symptoms usually subside sooner.

Laboratory Findings

Laboratory test results are nearly uniformly predictable. The serum bilirubin and alkaline phosphatase usually show a parallel rise of variable degree, thymol torbidity and cephalin flocculation tests are negative and transaminase levels are usually normal or slightly elevated.[6,7,10,14,15,34,36] Some patients may demonstrate more severe degrees of parenchymal cell necrosis, however. Orellana-Alcalde and Dominguez[22] reported transaminase levels over 300 in fourteen of their forty-seven patients. Where liver biopsies have been obtained[6,34] typical changes of cholestasis were described, i.e., canalicular bile plugs and centrilobular bile staining of liver cells, with some patients also exhibiting minimal scattered parenchymal cell necrosis. Inflammatory cells were rarely seen. Elevations of cholesterol, triglycerides and phospholipids are not uncommon.

Most patients with cholestasis of pregnancy (CP) have in their serum an abnormal lipoprotein which has been given the exotic abbreviation LP-X. LP-X is rich in phospholipids, especially lecithin, and unesterified cholesterol.[15,25] By precipitation techniques LP-X can be readily separated from VLDLs with which it shares antigenic determinants.[14] Seidel[30,31] and Neubeck & Seidel[20] have described the laboratory techniques for the identification of this lipoprotein, and Ritland[25] describes Seidel's tests as "simple, reliable, and sensitive". LP-X occurs also in patients with the rare inborn error of metabolism; lecithin-cholesterol acyl transferase deficiency,[14] and it also is seen in some other cholestatic conditions.[25,27,35]

Differential Diagnosis

The diagnosis of cholestatic jaundice of pregnancy requires, of course, differentiation from other conditions causing jaundice during pregnancy. These include disorders due to the pregnancy itself such as hyperemesis gravidarum, toxemia of pregnancy, obstetric acute yellow atrophy, and other conditions which may co-exist during pregnancy such as diseases of the gallbladder and common bile duct, toxic substances, hemolytic jaundice, hepatitis, and other infections.[4,36] Benign recurrent intrahepatic cholestasis may also be marked by jaundice during pregnancy and it shares many of the features of CP.[5] Factors in the history of the patient's illness, family history, laboratory test results, and if necessary, needle biopsy of the liver usually make the diagnosis not overly difficult. Differentiation from jaundice due to drug ingestion usually mimics the disorder most closely and must be inquired into carefully.

Therapy

Cholestasis of pregnancy does not usually require much in the way of treatment. When itching is a serious problem, cholestyramine will usually give complete relief, or relief adequate to allow the patient to sleep.[16,19] Espinoza et al[8] reduced the serum bilirubin levels to normal or near normal in most of their patients by the use of phenobarbital, though this drug has no effect on the cholestatic process per se.[13] Reid[23] suggests the use of Vitamin K parenterally to prevent postpartum hemorrhage secondary to deficiencies in coagulation factors, which may develop should the cholestatic process be unusually severe or prolonged.

Pathogenesis

A great deal has been learned regarding the pathogenesis of CP. There is apparently a metabolic defect which results in an alteration of steroid metabolism, and an abnormal response of the hepatic secretary mechanisms to a high level of estrogen.[6,13,28,29,32] The earliest manifestation of hepatocellular dysfunction in these patients is an inability to transport bile acids so that the serum level rises.[13] This readily explains the most prominent symptom that these patients have, that of pruritus, and the frequent relief that cholestyramine provides. The liver also fails to transport bilirubin into the bile.[6] These same changes occur in patients taking an oral contraceptive.[1,5,6]

Adlercreutz and Tenhunen[3] found on challenging patients with contraceptive medications that these changes were related to exposure to estrogens, not progestogens. Patients showing jaundice on oral contraceptives have been found to have the same symptoms, laboratory studies and liver histology as patients with CP.[6] Drill[6] also reports that of 32 patients with jaundice on an oral contraceptive agent, 24 had had CP in previous pregnancies. Sjovall and Sjovall[32] found six steroids in the plasma of patients with CP not found in normal women. They and Samsioe[28] and his group both feel that these changes may be due to bacterial action in the gut, or failure thereof, due to impaired enterohepatic circulation of the steroids and bile acids found in normal pregnancy. One of the steroids Sjovall and Sjovall found was a 17 alkylated estrogen which is the typical chemistry of estrogens in oral contraceptives and other drugs causing hepatic cholestasis.

One of the most intriguing aspects of this metabolism was a study reported by Samsioe, Johnson and Gustafson[29] in which they studied hepatic synthesis of lecithin. Under the influence of bile acids the normal liver manufactures a lecithin containing primarily palmitic acid (16:0) and oleic or linoleic acid. Estrogen stimulates production of lecithin containing stearic acid (18:0) and arachidonic acid. In women with a past history of CP it was remarkable that the lecithin in their serum had a lower content of palmitic acid (16:0) and a higher content of stearic acid (18:0) compared to normals. This suggests that women prone to develop CP may be more "estrogenic", a kind of biological marker of the disease. Whether this is an enzymatic manifestation of a genetic predisposition is not yet known.

Genetic Factors

That there is a genetic predisposition to this disorder seems likely from published reports. The majority of patients with CP are reported from Scandinavian countries, Finland and Chile.[3,24,37] Similarly most of the cases of jaundice while on oral contraceptives have been reported from the same areas.[22] Increasing numbers of cases of CP occurring in families have been reported.[5,34] dePagter et al.[5] and Orellana-Alcalde and Dominguez[22] raise the question as to whether cholestasis of pregnancy, pruritus gravidarum, jaundice due to oral contraceptive use, and benign recurrent intrahepatic cholestasis might not all share the same etiologic mechanisms and pathophysiology, as well as a tendency to familial occurrence. Benign recurrent intrahepatic cholestasis reported by Summerskill and Walshe[33] manifests the same symptoms, laboratory findings, liver histology, and benign course as does cholestasis of pregnancy. Johnson et al[14] show reasons why they believe pruritus gravidarum and CP are separate and distinct entities, but others[6,10,16] feel they are expressions of differing severity of the same syndrome, and the weight of evidence seems to support their opinion.

Effect on the Fetus

Though the syndrome of CP has consistently been a benign one for the mother it has not always been so for the fetus. Samsioe[29] stated that the "disease is considered harmless to mother and child" and Svanborg and Ohlsson[34] reported 22 cases with a benign course in all including the infant. In Thorling's original description,[36] however, there was a statistically significant shortening of the gestation period, and a decrease in the average birth weight of the infants born to mothers with CP. Others[7,9,10,16,18,23,24] have also reported a significant risk to the infant of premature births, intrapartum asphyxia, neonatal death, and diminished birth weight. Meconium staining of the amniotic fluid, a sign of neonatal distress, was found in 27% of births in CP as compared to 9% of normals.[10] Reid[23] feels strongly enough about this to suggest induction of labor at 37 weeks in all mothers with CP.

The mechanism for the stress on the fetus is not completely clear. Kater and Mistilis[16] studied the effect of maternal CP on fetal steroid metabolism. He found an impairment particularly of 16α-hydroxylation which normally occurs in the fetus. This resulted, in Adlercreutz and Tenhunen's studies, in reduced levels of 16 epiestriol and estriol with an increase in the precursers, including pregnanediols. Pregnanediols are high in the maternal blood and probably also cross the placenta into the fetal compartment. Hsia[12] demonstrated that pregnanediol was the most potent steroid inhibitor of glucuronyl transferase and Espinoza et al[8] demonstrated pregnanediols in the breast milk of mothers whose babies had prolonged neonatal jaundice. Disordered steroid metabolism may be a source of fetal stress, but infants born of mothers with CP do not show any tendency toward jaundice in the peripartum period, Laatikainen[18] showed that cholic acid and chenodeoxycholic levels were high in the cord blood of these infants and fetal distress was more frequent where these levels were high. Whatever the pathogenetic mechanisms, infants of mothers with CP bear careful watching.

Summary

A case of cholestasis of pregnancy is reported. The symptoms and signs are generally mild and manageable with cholestyramine and possibly phenobarbital when more severe. The postpartum course is benign with rapid resolution of evidences of disease though there is a tendency favoring recurrence in about half of the cases during subsequent pregnancies. There seems to be a strong genetic tendency reflected by the occurrence of the disorders in several members of the same family and a clustering of these cases in several countries. Estrogen seems to be the major pathogenic agent resulting in abnormal hepatic secretory mechanisms, which may relate in some way to the production of fetal distress.

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Cover Photograph

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Dr. Schultz is a Professor of Medicine at the University of Minnesota, Chief of Medicine at Hennepin County Medical Center, and an Associate Editor of MINNESOTA MEDICINE.

Minnesota Department of Health

Misconceptions about Possibly Rabid Animals that Have Bitten Humans

MICHAEL R. PETERSON, D.V.M., M.P.H.,[*] and BARRY S. LEVY, M.D., M.P.H.[†]

In order to determine methods currently being used by local health officers in Minnesota to manage possibly rabid animals that have bitten humans, we questioned 79 local health officers about how they would deal with three common situations. Forty-three (54 percent) of the respondents incorrectly stated that the appropriate duration of observation of a vaccinated dog or cat after it had bitten a human was longer or shorter than the recommended 10-day observation period. Seventeen (22 percent) of the respondents incorrectly stated that a vaccinated and an unvaccinated dog or cat should be observed for different lengths of time after having bitten humans. Thirty-eight (48 percent) of the respondents incorrectly stated that they would observe (rather than sacrifice and test) a skunk that had bitten a human. Local health officers and others responsible for rabies prevention may still have these and other misconceptions about methods of rabies prevention, and should periodically review current recommendations available from the Minnesota Department of Health.

RABIES IS A serious public health problem in Minnesota, which ranks third among the states in reported cases of rabies in animals. Approximately 300 confirmed cases occur annually, and no part of the state is considered free of rabies.[1] In addition, in 1975 a Minnesota resident died of rabies as a result of a cat bite.

Because of some recent changes in rabies prevention recommendations, the Minnesota Department of Health mailed to almost all practicing physicians in the state, including all local health officers, detailed information on prevention of rabies in humans in June 1974, June 1975, and August 1975. This information included recommendations on the management of possibly rabid animals that have bitten humans.

This report is based on an investigation we performed in the spring of 1976 to determine methods then being used by local health officers in Minnesota for management of possibly rabid animals that had bitten humans.

Methods

We mailed a questionnaire covering methods of observing possibly rabid animals that have bitten humans to 85 local health officers[‡] in Minnesota. Most responded by mail; we telephoned all nonrespondents and administered the questionnaire to them orally. We asked health officers to state how they would manage three common situations. In the first situation, concerning a dog or cat with a current rabies vaccination, we asked health officers to give information on the optimal duration and location of observation of the animal after the bite, the person responsible for observation, and, if the animal died before the end of the observation period, whether or not the head should be sent to a laboratory for rabies examination. In the second situation, concerning a dog or cat without a current rabies vaccination, we asked health officers to provide similar information. In the third situation, concerning a feral skunk captured alive, we asked health officers what the disposition of the skunk should be, and, if they believed observation was necessary, what duration of observation would be appropriate.

Survey Responses and Applicable Recommendations

Among the 85 local health officers whom we attempted to contact, there were 79 respondents, 41 by mail and 38 by telephone. Their responses were as follows.

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[†] At the time of this investigation, Acting State Epidemiologist, Minnesota Department of Health, and Medical Epidemiologist, Field Services Division, Bureau of Epidemiology, Center for Disease Control, United States Public Health Service. Dr. Levy is now Assistant Professor, Department of Family and Community Medicine, University of Massachusetts Medical School.

[‡] Of the 87 counties in Minnesota, 76 have county health officers, all of whom are physicians. Two of these 76 cover two counties apiece. For the remaining 11 counties without county health officers, we questioned health officers of the largest cities in these counties. We questioned health officers because they are responsible for public health at the local level and are often asked for advice on rabies prevention.

Address reprint requests to: Dr. Barry Levy, 128 Hollis Street, Sherborn, Massachusetts 01770.

First Situation

> A person has been bitten by a dog or cat which has a *current* rabies vaccination. The animal in question has not been exposed to or bitten by a known rabid animal.

Of the 79 respondents, 36 (46 percent) said the appropriate duration of observation of the animal after the bite was 10 days; 31 (39 percent) said a period longer than 10 days was appropriate, three (4 percent) said a shorter period was appropriate, and nine (11 percent) said no observation was necessary. All respondents replied that, if observed, the animal should be in the owner's home and observed by the owner for this period. All respondents agreed that the head should be sent to a laboratory for examination for rabies if the animal died before the end of the observation period.

A dog or cat with evidence of a current rabies vaccination is at minimal risk of acquiring rabies. A 10-day observation period for dogs and cats which have bitten people is the current recommendation of the Minnesota Department of Health, the Center for Disease Control, and the World Health Organization.[2-5] County health officers, physicians, and veterinarians should work together to insure that the pet has indeed been vaccinated and will be properly observed for the 10-day period.

Second Situation

> A person has been bitten by a dog or cat which has *not* been vaccinated for rabies. The animal in question has not been exposed to or bitten by a known rabid animal.

The responses we obtained were nearly identical to those in the first situation. We noted, however, that 17 respondents (22 percent) incorrectly stated that vaccinated and unvaccinated cats or dogs should be observed for different lengths of time.

All dogs and cats should be observed for 10 days, whether vaccinated or not.[2-5] Although unvaccinated dogs or cats are more at risk of acquiring rabies than vaccinated ones, the recommendation is the same regardless of the vaccination status of the animal. However, previously unvaccinated dogs or cats should be vaccinated at the end of the observation period. Clinical illness in such dogs or cats during the observation period should be evaluated as soon as possible by a veterinarian. If the animal dies during the observation period, it should be sent to a laboratory for examination for rabies.

Third Situation

> A person has been bitten by a skunk. The skunk is captured.

Thirty-eight (48 percent) of the respondents said that they would place the skunk under observation (for from five to 30 days), 37 (47 percent) said that they would kill the skunk and send it for laboratory examination for rabies, and four (5 percent) implied that they would do nothing since "there was no skunk problem" (sic) in their areas.

Skunks are the main reservoir of rabies in Minnesota, and skunks, foxes, bats, and raccoons are the primary wildlife reservoirs of rabies in the United States. If such an animal or a cow or a horse has bitten or otherwise potentially exposed a person to rabies, it should be killed immediately, and the head submitted to a laboratory for examination for rabies.[2-5] If the animal has escaped and no laboratory examination can be performed, postexposure prophylaxis should be given if: (1) the person has been bitten anywhere or licked on a mucous membrane, and (2) there is rabies in animals in that area.[2-5]

Discussion

The prevention of rabies in humans is an important public health function, which requires awareness and cooperation of health officers, other physicians, veterinarians, and other health care professionals. Approximately 4,300 animals are confirmed to be rabid in the United States each year.[1] Rabies in humans in the United States decreased from 20-25 cases annually in the late 1940s to one to three cases annually in the early 1970s;[1,6,7] however, when rabies does occur in humans, it is almost always fatal. Concern for the welfare of the bitten person must begin at the time he or she is exposed to a possibly rabid animal. Proper disposition of the animal is obviously of extreme importance.

As this report illustrates, many local health officers in Minnesota, which has much animal rabies, have misconceptions about the proper disposition of animals that have bitten humans. We presume that others with some responsibility for rabies prevention share these and other misconceptions about prevention of this disease. It is beyond the scope of this report to review current recommendations on rabies prevention, which are well stated in other publications.[2-5] We are hopeful that distribution of improved informational materials by the Minnesota Department of Health and renewed efforts by local health officers, other practicing physicians, veterinarians, and others involved in rabies prevention can eliminate these misconceptions.

Acknowledgments

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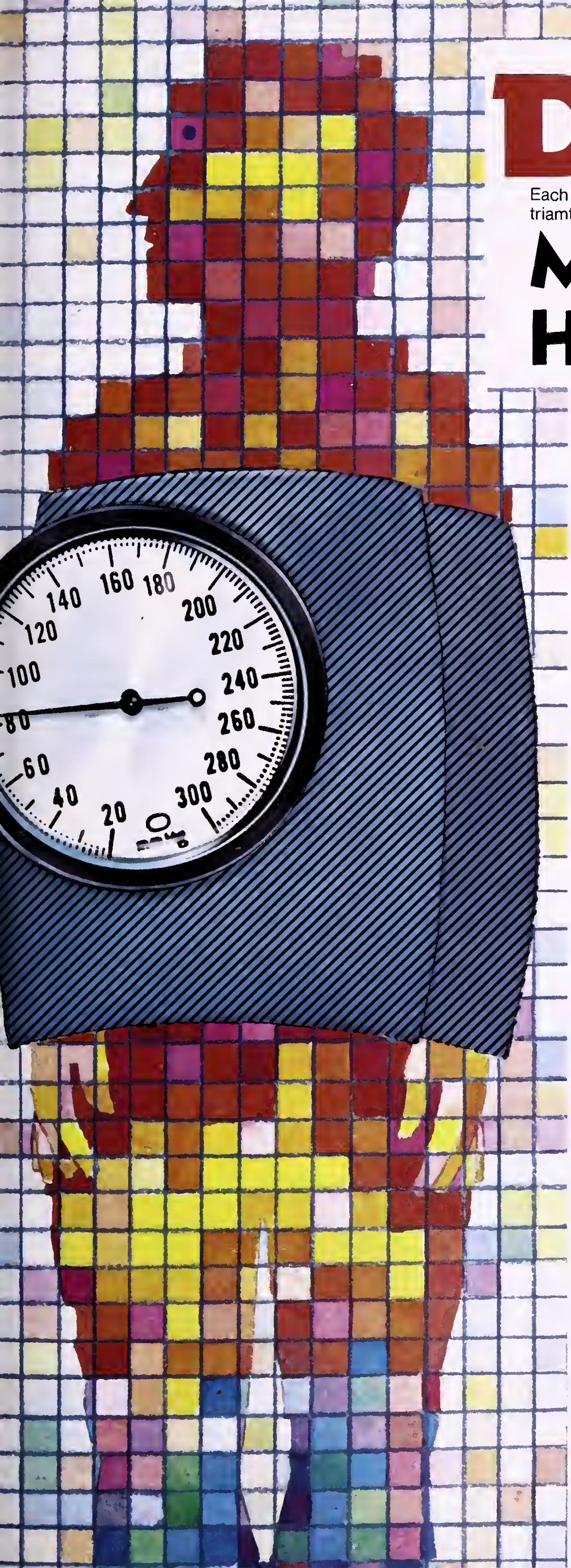

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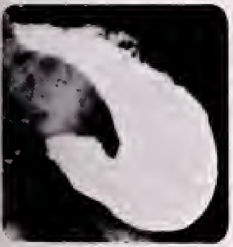

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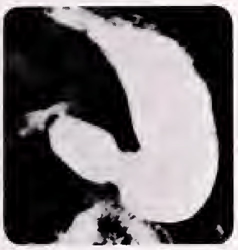

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King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia, increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling, severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage Bentyl 10 mg. capsule and syrup: *Adults* 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children* 1 capsule or teaspoonful syrup three or four times daily. *Infants:* ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults:* 1 tablet three or four times daily. Bentyl Injection: *Adults:* 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

Injectable dosage forms manufactured by CONNAUGHT LABORATORIES, INC., Swiftwater, Pennsylvania 18370 or TAYLOR PHARMACAL COMPANY, Decatur, Illinois 62525 for MERRELL-NATIONAL LABORATORIES, Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215, U.S.A.

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Legislation

Minnesota "Brain Death" Legislation: A Step Forward . . . Or Backward?

JOHN M. BURNS, M.D.* and JOHN S. HAMLON, M.A.†

I. Ethical and Medical Considerations

Background: Complex and Volatile

Minnesota law-makers may soon debate, for the second time, the complex and volatile issue of ''brain death'' legislation.

The issue is complex, not only because two distinct professional disciplines (medicine and law) are involved, each with its own responsibilities and viewpoints, but also because opinions on the desirability of ''brain death'' legislation cover the *pro-con* spectrum in both professions. Even within respective *pro* and *con* camps, one is hard pressed to find two identical opinions on why ''brain death'' should or should not be statutorily defined.

The issue is volatile because it involves the visions (and emotions) of two rapidly diverging ethical systems which stem, respectively, from secular humanism and Judeo-Christianity. Less than a half-century ago, American humanism largely reflected the ethical norms found in a predominantly Judeo-Christian culture. In *Humanist Manifesto I* (signed by such notables as John Dewey, chief architect of the present American public school system), the fifteenth ''affirmation'' states:

> . . . humanism will: (a) affirm life rather than deny it; (b) seek to elicit the possibilities of life, not flee from it; and (c) endeavor to establish the conditions of a satisfactory life for all, not merely for the few.[1]

When isolated from the explicit, atheistic assertions preceding it, this affirmation does not conflict with the Judeo-Christian view that human life is precious and that one's moral obligations to others is to be grounded in love and concern for all.

Forty years later, in 1973, *Humanist Manifesto II* was signed by 114 individuals of ''prominence and distinction,'' including Isaac Asimov, Francis Crick, and Alan Guttmacher. This update of *Humanist Manifesto I* was dramatic because it chose to deal with evolving problems facing mankind (ecological damage, overpopulation, dehumanizing institutions, totalitarian repression, nuclear and biochemical disaster) in situational and utilitarian fashion. ''Moral values,'' say the authors of *Humanist Manifesto II,* ''derive their source from human experience. Ethics is *autonomous* and *situational,* needing no theological or ideological sanction. Ethics stems from human need and interest. To deny this distorts the whole basis of life.''[2]

Given this set of moral and ethical ground rules, it is not surprising that this latest manifesto asks society to recognize the individual's right to birth control, abortion, divorce, and any sexual proclivity expressed between consenting adults. But it sees humanistic freedoms extending well beyond the area of human sexuality:

> To enhance freedom and dignity the individual must experience a full range of *civil liberties* in all societies . . . [including] a recognition of an individual's right to die with dignity, euthanasia, and the right to suicide.[3]

It is obvious that today's humanists have come a long way in offering pragmatic solutions to the true ''democratizing'' of society. And, in our opinion, it would be difficult to underestimate the tremendous influence that modern humanism has had on secular, as well as religious, America. Modern humanistic ethics has largely replaced Judeo-Christian ethics as the backdrop for federal and state policy-making in health, education, and welfare, while a substantial segment of the Judeo-Christian populace has either sanctioned this switch or remained noncommittal.

Respect-for-life groups are well aware of secular humanism's growth and its present influence (specifically concerning sex-education, abortion, and euthanasia), and they seek at least to stop this influential trend, if not actually reverse it.

Neither advocates for legal euthanasia nor certain respect-life-groups see ''brain death'' legislation as simply a *tête-a-tête* between medicine and law, but, rather, as a first step towards the legalization of voluntary (and, possibly, non-voluntary) euthanasia. Euthanasia advocates are for this kind of domino reaction; respect-for-lifers are definitely against it. The ''battle lines'' are drawn, and Minnesota legislators will have to debate the ''brain death'' issue in the no-man's-land between these two positions, keeping in mind that, while they sift through the complexities of the *pro* and *con* arguments, they will not be in a philosophical vacuum.

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Lawyer William H. Manning and associate professor of law Howard J. Vogel recently co-authored an article entitled "The Case for 'Brain Death' Legislation: A Response to the Critics".* In reviewing and answering the more prominent arguments against a Minnesota "brain death" act, their expressed hope was to clarify misunderstandings concerning "brain death" legislation and to, thereby, defuse the emotional volatility surrounding the issue, itself.

Part I of this series will examine and comment on several important points raised by Manning and Vogel; Part II will compare the Uniform Brain Death Act with the "brain death" definition proposed by the American Bar Association. Our hope is that this course of action will further clarify a most difficult subject.

Critique of Manning-Vogel Article

1. Manning and Vogel correctly state that the "brain death" dispute raises "important theological and philosophical questions about life, death, the quality of life, and the nature of human personality. . . ."[4] However, they go on to say why they will not deal with such questions:

> [These questions] have provided the substance of intellectual argument throughout the centuries. Our society has not yet found answers to these questions, and we seriously doubt whether ultimate answers to such questions can be perfectly discovered by human reason or intuition.[5]

Their reluctance to wade into the philosophical and theological dimensions of the "brain death" issue is quite understandable, especially within the confines of a single article. Nevertheless, we are uncomfortable with the rationale behind this reluctance for two reasons. First, it leaves the mistaken impression that, over the last three millennia, man has not developed any philosophical or theological insights which would assist him in making modern ethical judgments on matters of life and death. If man has, as we believe, considerably deepened his intellectual and spiritual awareness of what gives human life its special quality, then this awareness — though not "ultimate" — can help formulate what is truly good for him and society.

Second, this rationale is reminiscent of that used in the Supreme Court's decision of January 22, 1973, when it spoke about the beginning of human life:

> We need not resolve the difficult question of when life begins. When those trained in the respective disciplines of medicine, philosophy, and theology are unable to arrive at any consensus, the judiciary, at this point in the development of man's knowledge, is not in a position to speculate as to the answer.[6]

By reasoning this way, the Supreme Court *did* "resolve" the "difficult question" of when human life begins by legally considering the unborn as non-persons. In this case, *not* to decide was to decide.

In effect, Manning and Vogel's rationale, if accepted, neutralizes the need to distinguish between humanistic and Judeo-Christian presuppositions concerning the nature of man.

2. Manning and Vogel argue that because of "dramatic advances in medical science . . . the traditional criteria for determining the occurrence of death — absence of pulse and respiration — are no longer, in all cases, reliable . . . For that reason, we believe that society must come to grips with 'brain death' through enacting that concept into legislation."[7]

The traditional way of educating the layman on medical matters has been through personal contact with the physician or physicians handling a particular case. This lay-professional interchange best helps the layman "come to grips" with medical realities that affect him or those close to him. Statutorily defining death will, in no way, abrogate the physician's responsibility to explain to the layman what clinical criteria determine death nor will it obviate the need for such an explanation.

When it concerns medical concepts, the best teachers remain the physicians, themselves. However, they must first know the medical issue well and be confident in their conclusions before they can pass their knowledge and confidence on to the public.

The problem is that a significant number of physicians do not have adequate knowledge of "brain death" criteria and require considerable education in the medical skills necessary for application. Nor have they had the chance to digest all the possible legal and medical ramifications (some of them rather subtle) of "brain death" legislation. Until the medical community is adequately educated, the discussion of "brain death" legislation — especially as an educative spur for the public — is premature. To legislate a concept, when those responsible for applying the concept's criteria are largely unaware of the criteria involved, is to openly invite confusion and even hostility from those who feel that medically educating the public is an integral part of the art of medicine and a responsibility that cannot be delegated, even to the legislature.

3. In answer to such an argument based on prematurity, Manning and Vogel point out that:

> Those who must act based upon whether or not a person is dead currently do so in a terrain with no legal maps. In absence of clear guidelines, accepted under law, these persons needlessly face the possibility of law suits which can only deter them from accepting their responsibility to declare "brain dead" persons dead. Official action, not mere discussion of the issues, is required to eliminate the existing conflict between current medical practice

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*Minnesota Medicine, February 1979.

and present law.[8]

Such an altruistic concern for the physician is truly commendable, but we wonder whether "official action" by the legislature would actually put an end to possible litigations against physicians involved in "brain death" cases.

Let us look at a hypothetical case. A young boy is struck by an automobile. He is unconscious, has obviously suffered a head injury, and is rushed to an emergency hospital. He requires respiratory support, first by mouth-to-mouth, and subsequently by a mechanical respirator. A bedside cardiac monitor shows a normal rhythm and cardiac action, and his cardiogram is normal. But he is totally unresponsive. You, the physician, tell the boy's parents that his injuries are exclusively to the brain, quite extensive, and of great severity. The next day, after an all-night vigil, and after repeated consultations by neurologists and neuro-surgeons, you tell them that their son's brain injury is so severe that, in essence, the brain has been destroyed, that his oxygenation is totally dependent on the respirator (since his respiratory center in the brain has been destroyed) and that nothing can be done. You then tell them that their son is dead and, in view of this, the respirator should be discontinued. If they accept your diagnosis, and the respirator is discontinued, the tragedy is over. It is a great loss, but there is nothing that could be done. But what if they do not accept the diagnosis? What if they ask, "Is he really dead?" "Can't anything be done?" "Shouldn't another opinion be sought?" "What about Rochester?" Will you then say that the law is on *your* side, that the boy's death is legal, regardless of their feeling, and that the respirator has to be turned off because their son is legally dead and, by law, you, the physician, *must* make the pronouncement? The application of the law in a contested situation such as this, can easily erode the basic ethic of the traditional doctor-patient relationship. A physician, recognizing that there is opposition in this situation, would not want to force the pronouncement on the parents. It will only be a matter of a few days until cardiac function ceases to occur because one cannot indefinitely sustain a brain-dead body as a heart-lung preparation. To force the legality of "brain death" upon a family in a situation where they will not accept the medical diagnosis will invite litigation, even though the law purports to back the physician.

In such a dilemma, not only will the physician feel pressure from two seemingly intractable forces, but the parents will not have the traditional recourse of another medical opinion or simply the time to understand that their son is, in fact, dead.

We are not unaware or unconcerned about the present possibility of lawsuits against physicians who become involved in "brain death" cases. The question is, will a "brain death" act eliminate (or stimulate) litigation proceedings? The doctor-patient relationship is delicately balanced between empathy and trust. And in such relationships there is vulnerability on both sides. When the doctor's vulnerability is assuaged by the law, the patient (or, in the case of "brain death," the immediate family) may well try to use the law to reestablish an equilibrium. When this happens, empathy and trust will erode.

When listening to the argument that physicians should be protected from the possibility of "brain death" lawsuits, one wonders what the litigation "prognosis" would be if members of the Minnesota law profession were as intimately acquainted with and sympathetic to the physician's plight as are Manning and Vogel. Perhaps educating other lawyers about the problems facing the physician in "brain death" cases would alleviate some of the unnecessary and undue pressure on the medical profession.

There is, of course, another side to this same coin. Joseph Fletcher, a "quality-of-life" philosopher and advocate of abortion and active euthanasia,[9] gave the keynote address during graduation ceremonies at the University of Minnesota Medical School in 1976 (an indication that Minnesota medical educators and students are interested in, if not influenced by, the humanistic and utilitarian view of man as simply a biomedical phenomenon).

Four years before this address, Fletcher wrote an article entitled, "Indicators of Humanhood: A Tentative Profile of Man." In this unabashed argument for weeding out nonpersons, Fletcher establishes "positive" criteria for meaningful human existence:

(1) Minimal intelligence. (Below a 20-mark in a standard Stanford Binet I.Q. test would indicate "not a person.")
(2) Self-awareness. (Those with irreversible damage to the brain cortex would not qualify.)
(3) Self-control. (An individual not controllable by others, or by himself, is not a person ethically or legally, unless his condition can be "rectified medically.")
(4) A sense of time, futurity, and the past.
(5) The ability to relate, love, communicate, be curious, change, etc.
(6) Neo-cortical function. ("But what is definitive in determining death is the loss of cerebration, not just of any or all brain function. Personal

> reality depends on cerebration and to be dead 'humanly' speaking is to be ex-cerebral. . . .'')[10]

One can only speculate on what percentage of future medical practitioners will abandon the Hippocratic Oath in favor of a medico-ethical stance similar to Fletcher's. If there should be such a shift in medico-ethical ideals, then it could be argued that a ''brain death'' act, properly worded, would ''lock in'' a sound definition of death and, thereby, protect the public from future ''quality-of-life'' physicians.

This argument would be compelling if the medical profession were the only professional group susceptible to such ''quality-of-life'' criteria. But the fact is that a humanistic push for ''quality'' can be found in virtually every professional endeavor, including the teaching of Christian seminarians. If the majority of the public sector, somewhere down the road, opts for secular humanism, then active euthanasia will be accepted as a necessary part of life, and physicians will be expected to technically handle the severing of nonpersons from society. At such time, a ''sound brain death'' definition could easily be modified to reflect the dictates of the majority.

A rather chilling substitute for redefining death is offered by lawyer-doctor H. Richard Beresford. In a commentary entitled, ''The Quinlan Decision: Problems and Legislative Alternatives,'' Beresford suggests that instead of attempting to redefine death, the legislature might ''define criminal homicide so as to *exclude* conduct by a physician which leads to the death of a *noncognitive* patient (emphases ours).''[11] This amendment to criminal law would concede ''that withholding or removing life-support measures from a brain-damaged patient is homicide but [would exempt] from criminal responsibility the physician who practices such compassionate neglect.''[12]

However, there is another concession contained in this proposed statute which is very interesting and germane to our argument:

> Creating a statutory exemption from homicide does not in itself protect a physician from civil suit. But one can assume that the physician who elects to reduce care for a brain-damaged patient would, as is customary practice now, obtain the prior consent of family or guardian. Similarly, if death is redefined *to include loss of cognition* and a physician terminates care of a noncognitive patient, the *risk remains of a civil suit for wrongful death*. The physician would prevail, however, unless there was proof of negligence in the appraisal of the patient's neurological status (emphases ours).''[13]

This brings us back to the original question in this section: Would a redefinition of death (even to include noncognition) protect the physician from litigation? Apparently there are lawyers who believe it would not.

And it would be well to note that where doctors are now vulnerable to lawsuits based on everything from ignorance to greed, the future could add another motive, fear. As Dr. Louis R. M. Del Guercio so aptly forewarns:

> Confidence in and reverence for the physician dates from the historic separation of the power to kill and the power to cure stated clearly and concisely in the Hippocratic Oath. . . .
>
> Hippocrates recognized the necessity of such assurance to patients in the fifth century before Christ. Once we as physicians start making decisions regarding who is or who is not worthy or deserving of our best efforts, we revert to black and white magic. Physicians will then see again fear in the eyes of their patients — not fear of pain or fear of death, but fear of the physician.[14]

4. Manning and Vogel do not believe that a ''brain death'' act constitutes a first step toward euthanasia

> since everyone agrees that it is to be applied to dead persons, not to living persons when deciding whether or not their lives should be allowed to end, as the proponents of passive euthanasia suggest, or to be terminated by medical intervention, as the proponents of active euthanasia suggest. . . . Brain death is only a step toward euthanasia if we lack, now and in the future, the ability to keep straight the difference between the questions, ''Is this person dead?'' and ''Should this person be allowed to die?''[15]

The distinction between these two questions is vital, to be sure. That is precisely why so much time and effort has been spent developing ''brain death'' criteria as well as exact wording in ''brain death'' legislation.

As Manning and Vogel suggest, a properly worded ''brain death'' statute cannot, by itself, open the doors to passive or active euthanasia. However, the intent behind such a statute is as important as its wording. Is the intent to protect physicians from disgruntled or unscrupulous relatives? Is it to educate society? Is it to preclude euthanasia advocates from getting the first legislative toehold? Is it to upgrade a lagging organ transplant program? Is it to get the public used to the idea of ''brain death'' so that acceptance of ''neocortical death'' will not be such a quantum leap for future legislators?

When Minnesota legislators debate the efficacy of a ''brain death'' statute, they will not only have to sort out the myriad arguments, both for and against, but also discern the intent behind those arguments. The wording of a ''brain death'' act, if actually passed, may or may not signal the proponents' intentions but the future effects of such an act will be regulated in large part by its *raison d'être*.

5. The problem of ''medical precedence'' is not discussed by Manning and Vogel. To have a law tell the physician when he should or should not pronounce a person dead is unprecedented. Will the law then feel it necessary to extend its influence into areas of medicine that, in the future, become problematic or sensitive? Although we cannot be certain that this *will*

happen, we must be aware that such a precedent paves the way for similar legislative action. Underlying any legislative action on medical matters is the implication that proper medical practice can best be determined by what is legal. *Such an implication will leave an indelible imprint on the future practice of medicine in the state of Minnesota.*

Summary

In critiquing "The Case for 'Brain Death' Legislation: A Response to the Critics," we have sought to explore and comment on those responses by the authors which concerned us the most. To reiterate, we feel that (1) the *absence* of "ultimate" answers to "important theological and philosophical questions about life, death, the quality of life, and the nature of human personality" should not deter us from drawing upon the intellectual and spiritual resources that we *do* have; (2) the best (not necessarily the fastest) way to help society "come to grips" with complex medical issues, such as "brain death," is through a personal and compassionate tutorship offered by individual physicians, many of whom need time to become adequately aware of "brain death" criteria and educated in the medical skills necessary for application; (3) a "brain death" statute would not necessarily eliminate litigation and could erode the empathy-trust relationship between doctor and patient; (4) the intent behind a "brain death" statute would largely determine the statute's future as a stepping stone to euthanasia; and (5) a "brain death" statute would set an extraordinary precedent for legislative involvement in medicine.

After listening to the arguments for and against a "brain death" act, should the Minnesota legislature still decide to define "brain death," the semantics of the definition will be crucial. In Part II of this series we will (1) analyze and compare two different proposals, the Uniform Brain Death Act and the definition accepted by the American Bar Association, and (2) attempt to answer the question "How definitive should a 'brain death' definition be?"

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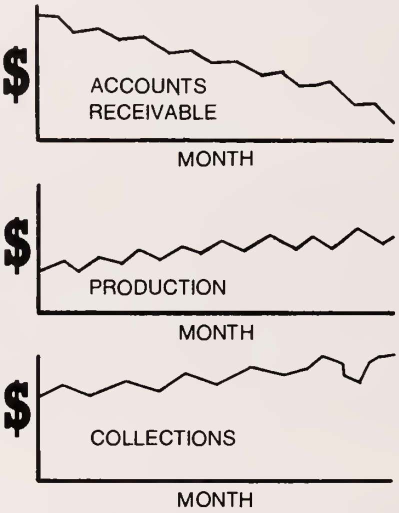

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Special Article

Metropolitan Medical Office Building Fire

The Event and its Consequences

DAVID L. MOODY, M.D.* and JIM THALHUBER†

MOST HOSPITALS HAVE disaster plans that detail how to provide care for crisis victims. But what does a hospital do when the "crisis" is a medical office building fire across the street and the "victims" are physicians, dentists, and professional people who suddenly lose their regular office sites, records, and equipment?

The Answer

At Metropolitan Medical Center (MMC) in Minneapolis, the answer was to provide temporary office space in the hospital and equipment and support services for more than 100 physicians who needed help after fire routed them from their offices on January 14, 1979 in the Metropolitan Medical Office Building. Prompt actions by hospital personnel minimized the impact of the disaster, enabling these physicians to continue their practices so their patients could receive care.

The Fire

The five-alarm fire in the office building, a thirteen story structure and one of the largest medical office complexes in Minneapolis, started about 2:15 a.m. on that Sunday morning. While the blaze caused no fatalities and only a few fire-fighting injuries, the fire completely shut off access to the building and adjacent parking ramp. Flames gutted the first three floors and mezzanine level, and smoke and soot damaged floors four through twelve. Elevator, heat and electrical systems were knocked out. Smoke and water-run off filled the lower level of the building, as well as the tunnel connecting it to the hospital. The fire's immediate consequences were to shut down completely a large medical office building, its connected 600 car indoor parking ramp, and one adjacent 35 car parking lot.

Because of the intensity of the blaze, the heavy smoke and the thousands of gallons of water poured on the building, it was fortunate most patient records were unharmed. A small number of records left on desk tops were lost and others singed on the edges, but the patient

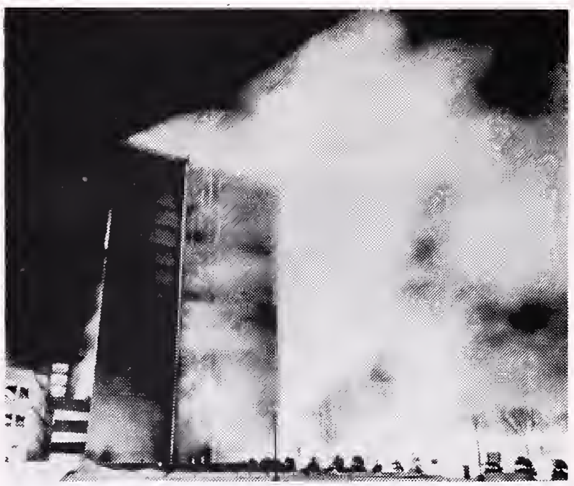

Fig. 1 — Smoke bellowing from southside of Metropolitan Medical Building a few hours after start of fire. (Reprinted with permission from the Minneapolis Tribune.)

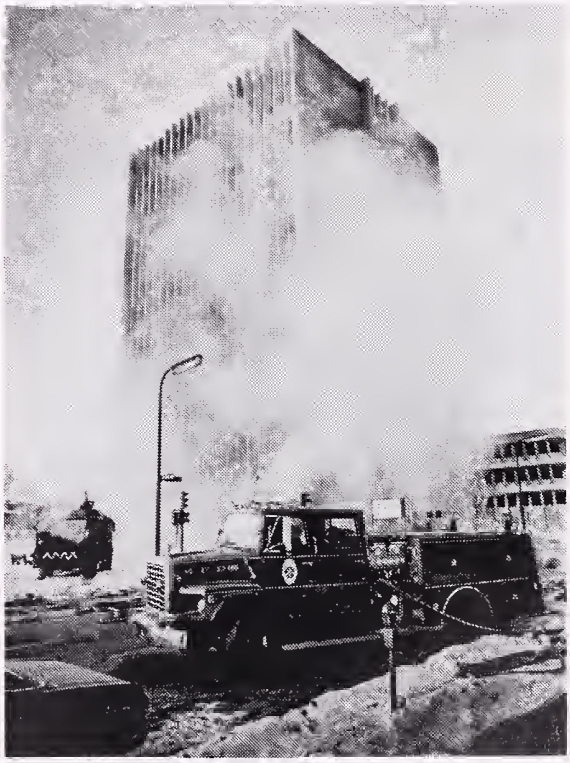

Fig. 2 — North side of building at mid-morning with fire engines blocking street. (Reprinted with permission from the Minneapolis Star.)

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* President of Medical Staff of Metropolitan Medical Center, Minneapolis.

†Director of Community Relations, Metropolitan Medical Center.

records of only two physicians were completely destroyed.

The Response

Even before the flames were completely extinguished, MMC's administrative staff was at work early Sunday morning, planning how the hospital could best help physicians displaced by the fire.

Information Center

One of the first steps was to establish an information center. As physicians arrived to assess the damage or called the hospital to find out what had happened, they were asked to call or visit the information center to convey their office space problem. As requests were received, they were forwarded to a top management team representing several hospital departments. This team analyzed the space available in the hospital and what areas might be readily cleared, and the minimum space and equipment required by the physicians. The team then began matching the needs of the physicians with the limited space available.

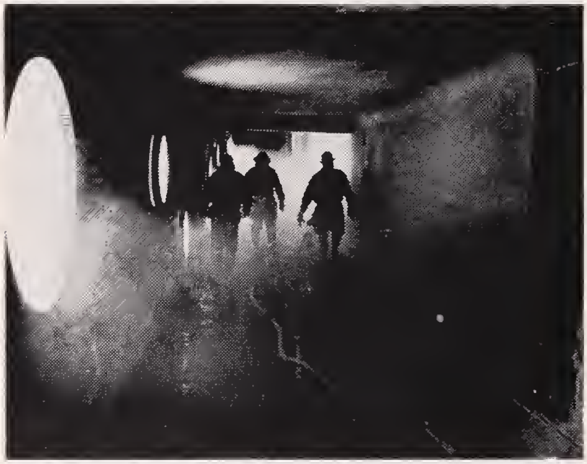

Fig. 3 — Partially water and smoke filled tunnel connecting office building with Metropolitan Medical Center. (Reprinted with permission from the Minneapolis Tribune.)

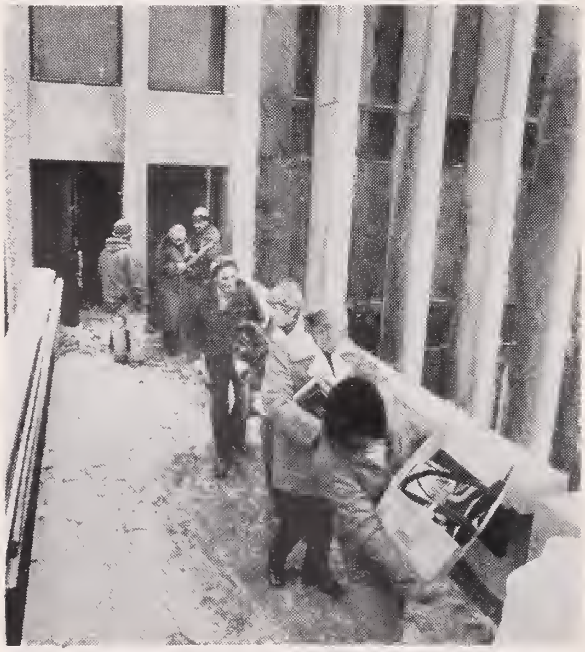

Fig. 4 — Doctors and office personnel moving equipment and records from offices to temporary headquarters.

Secondary Office Locations

While many physicians were able to move to secondary office locations in the suburbs or other downtown offices, dozens of doctors requested hospital space within hours of the fire. (The number eventually grew to 107. All told, about 150 physicians were affected, or almost 10 percent of the physicians of Hennepin County.) Much of the space found for the physicians was in the upper floors of the former Swedish Hospital which was unoccupied or being used for storage. Other available areas were found scattered throughout the complex. Some employees vacated their offices to make room for the physicians by doubling up with others in the hospital.

Equipment and Furnishing

But finding space was only a part of the job. Nearly all of the doctors required basic medical equipment and furnishings in order to open their temporary offices, since much of their own equipment was either inaccessible immediately after the fire or needed repair, cleaning or replacement. While some members of the MMC management team worked on space allocation, others prepared to meet the immediate office needs of the hospital's new tenants.

Basic office equipment (desks, chairs, examination tables and other supplies) was gathered from throughout the hospital, and calls were placed to other local hospitals and equipment vendors. Arrangements were made to have the telephone lines from the physicians' former offices re-routed to newly installed phones in the temporary locations.

End of First Day

As the day drew to a close, temporary office locations were assigned and plans were well underway to provide for other physician needs. While these decisions were being made, a group of physicians were busy telephoning those medical staff members who weren't affected by the fire in an attempt to obtain additional space and equipment. Calls also started coming in from other physicians in the area, offering to help in any way they could. These offers were posted in the medical staff lounge and on bulletin boards.

Sunday was only the first day of long hours, difficult decisions and hard work by MMC personnel, the physicians and their office staffs. In the days following the fire, temporary sites were cleaned and secured, equipment gathered from around the city, telephones installed, supplies distributed and other plans developed to ready the temporary office sites for patient visits. The hard work and long hours paid off — some physicians began seeing patients on Monday, the day after the fire, and most were back in business by Wednesday.

Temporary Quarters

The temporary office sites were spartan, but functional. Hallways lined with chairs served as waiting rooms, sheets strung from wall to wall sectioned off exam areas, and outside windows lacked drapes or curtains. As one physician commented, it was "a little like camping out, but I'm really quite pleased with the space." Another said, "Isn't it wonderful to practice Medicine without paperwork again?"

Support Services

Providing support services was another essential element of the relocation process. Through memos and daily rounds to each office location, physicians and their office staffs were informed on how to obtain linen, get mail, have equipment cleaned or sterilized and order other necessary supplies from the hospital's storeroom.

The hospital's ancillary services — pharmacy, laboratory, x-ray and others — also had to gear up to meet the needs of the physicians' patients.

Physician Reaction

Physicians reacted favorably to the hospital's efforts. "The fact that we were here and seeing patients on Monday is remarkable," said a physician, "considering all that had to be done." Although conditions were chaotic for several days after the fire, another physician summed up the feelings of many of his colleagues when he remarked, "I deeply appreciate the efforts of everyone involved . . . I often wonder what we would have done if the hospital hadn't stepped in and helped us. Where would we have gone? What would we have done?"

Helping Patients

As MMC proceeded to help physicians set up their temporary locations, patients began trying to get in touch with their doctors to confirm appointments and find out if their medical records were still intact. These calls were directed to the information center, which took messages and relayed new office locations to more than 3,000 patients. in the first few days after the fire.

To further help those patients find their doctors, MMC placed a public service announcement in both the city's major daily newspapers which listed the names and locations of the physicians in MMC quarters. Signs were prepared and posted outside the hospital, in lobbies, on floors and on doors to help in the communication effort. A special information desk was even set up in the main lobby to help direct patients to offices.

Tenant Meetings

MMC also cooperated with Kraus-Anderson, Inc., owners of the medical office building, in keeping physicians up to date on the condition of the building. Two tenants' meetings were held at MMC to relay information on how to gain access to records and equipment trapped in the building, how remodeling and reconstruction were progressing, and the services available through the hospital. Daily memos from Kraus-Anderson were hand-carried by MMC personnel to temporary office locations.

Moving Back

For many tenants, the stay at MMC was a short one. About 70 percent of those officed in the hospital who had been located on the upper floors of the office building were able to move back into their suites within two weeks after the fire. For those officed in the gutted portions, their stay at MMC may last another several months.

Even though the dust has not yet settled from the January 14 disaster, some long-run benefits have already become apparent. Fire alarms and smoke detectors, not required when the building was constructed in 1969, are scheduled to be installed in some areas of the building. Steps are being taken to increase building security. Physicians have come to realize the importance of having adequate insurance. Several physicians said they did not think insurance coverage was necessary because of the building's fireproof construction. Others simply did not even think of buying insurance. Some physicians had neither accounts receivable insurance nor duplicate financial records in a secondary location; others had failed to annually reappraise the insurable value of their older equipment and leasehold improvements and so were covered for only a small percentage of today's replacement cost.

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Obstetrics-Gynecology

Colposcopy Experience
at St. Louis Park Medical Center

ARLYN A. HAMANN, M.D.*†

Nearly 600 women have been colposcoped by the Obstetrics-Gynecology Department at the St. Louis Park Medical Center. This discussion presents the correlation between the Pap smear class and biopsy diagnosis in these patients. It also presents the various treatment modalities used in treating the abnormalities encountered.

MEDICINE HAS BEEN a dynamic changing science as greater understanding of disease is achieved. This has certainly been the case in the diagnosis and treatment of cervical carcinoma-in-situ and its precursors. Only a few years ago carcinoma-in-situ was treated with radical or modified radical hysterectomies. Now in many cases, especially in young women who wish to preserve fertility, treatment consists of simple cervical conization or even cryoconization.

Colposcopy has been an important tool in the diagnosis and understanding of early cervical neoplasia. The Obstetrics-Gynecology Department at the St. Louis Park Medical Center began doing colposcopy in 1973. Since that time we have colposcoped nearly 600 women. Although most of these were done for the evaluation of abnormal Pap smears, others were done for a closer view of observed cervical abnormalities. Still others were done for the evaluation of women who had had intrauterine exposure to diethylstilbesterol.

In tabulating our colposcopy experience, 568 cases were appropriate for inclusion into the study. Many patients had two or more abnormal Pap smears prior to being colposcoped. A number of patients also had repeat colposcopically directed biopsies because of persistently abnormal Pap smears after initial colposcopy had failed to reveal significant lesions. For the purpose of categorizing results, the worst Pap smear result obtained and the most severe histologic changes mentioned on a pathology report were used.

Table 1 summarizes our overall findings. There were 435 cases where the most severe Pap was a Class II. Many of these were colposcoped after only one abnormal Pap while others had repeated Class II smears prior to colposcopy. I would consider significant those with moderate dysplasia or worse. Of the 435 there were 133 with moderate dysplasia, 78 with severe dysplasia, and 30 with carcinoma-in-situ.

In the group of Class III smears there was 31% incidence of malignancy. Among 120 cases, there were 20 moderate dysplasias, 44 severe dysplasias, and 36 carcinomas-in-situ plus one adenocarcinoma of the endometrium.

Only 13 Class IV Pap smears were encountered. All of these had significant abnormalities with one severe dysplasia, 10 carcinomas-in-situ, one invasive squamous cell carcinoma, and one adenocarcinoma of the endometrium.

The total incidence of carcinoma in the entire study was 13.9%.

TABLE 1
Colposcopy Results of 568 Patients

Pap	No Lesion Seen or Neg. Biopsy	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	Carcinoma in-situ	% Malig.
II (435)	84	110	133	78	30	6.9
III (120)	4	15	20	44	37*	30.8
IV (13)	0	0	0	1	12†	92.3
TOTAL	88	125	153	123	79	13.9%

*One Adenocarcinoma of Endometrium.
†One Adenocarcinoma of Endometrium, plus One Invasive Squamous Cell Carcinoma.

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*Department of Obstetrics-Gynecology, St. Louis Park Medical Center, Minneapolis, Minnesota.

†Clinical Instructor, Department of Obstetrics-Gynecology, University of Minnesota.

Frequently Class II Pap smears were qualified with terms such as "weak" or "minus" and "strong" or "plus." The finding of a "strong Class II" or "Class II plus" smear certainly proved significant with a carcinoma-in-situ rate of 17.5%. The smears reported as a regular Class II had a 5.8% in-situ carcinoma rate and the weak Class II smears had no in-situ carcinomas. These findings are illustrated in Table 2.

Table 3 compares the pathology results of colposcopically directed biopsies with those of subsequent cervical conizations. There are many uncontrolled variables in this retrospective analysis but several observations can be made. Cervical conizations performed following a colposcopic biopsy which showed only mild changes were done either because a lesion could not be completely visualized or because the findings did not seem compatible with the degree of Pap smear abnormality. A number of conizations were done because of a persistence of Pap smear or colposcopic abnormality following cryoconization of the cervix. There were 28 instances in the 99 cases where the findings at conization were less severe than those diagnosed on colposcopic biopsies. This probably is explained either by the removal of the most significant portion of the lesion at colposcopy or by a regression secondary to reaction from the biopsy.

It generally is considered significant if changes found at conization are greater than one step more severe than changes on colposcopic biopsies. Three cases of moderate dysplasia at colposcopy followed by carcinoma-in-situ changes at conization were noted. A specific review of these cases showed that two of them had lesions which were not completely visualized at colposcopy and that the conization was done for that reason. The other case was one in which there was a persistence of Pap smear abnormality following previous cryotherapy.

The therapy of the various lesions is presented in Table 4. For the most part the degree of treatment correlated well with the severity of the lesion. The hysterectomies in the mild lesions were done for other gynecologic indications a short time following the colposcopy. Cervical conization was used as treatment for carcinoma-in-situ in young women who wished preservation of fertility. Cervical conization done just prior to hysterectomy is not included in these figures. The cone biopsies in the mild lesions were done either because of repeated abnormal Pap smears with no visible colposcopic lesion or because a portion of a lesion extended into the cervical canal and could not be completely visualized. Conservative therapy such as cryotherapy or isolated biopsy must be restricted to those lesions in which the margins are clearly seen colposcopically.

Of special interest are the cases of carcinoma-in-situ which were treated with cryoconization or biopsy only. These were special cases, as where the diagnosis was made in early pregnancy. Following delivery, when the cervix was recolposcoped only a minor lesion or no lesion at all was found. In these cases there either was spontaneous resolution of the lesion or the lesion was so small as to have been entirely removed at the time of the initial biopsy. This later example points out how specific colposcopy can be in defining a small isolated lesion.

The majority of the cryoconizations were done using the freeze-thaw-refreeze technique. There were a significant number of persistent lesions which required refreezing or other treatment. Stressing the importance of follow-up Pap smears is essential, especially in the women with significant lesions. In the past year we have switched to using nitrous oxide rather than carbon dioxide as the freezing agent because of the lower temperature obtained, in an attempt to reduce the number of patients needing retreatment.

There are a number of advantages in utilizing the routine use of colposcopy for the evaluation of abnormal Pap smears:

The first is an increased accuracy of diagnosis as compared to random cervical biopsies. When the lesion can be visualized, specific biopsies can be taken with reasonable assurance that the worst area on the cervix has been sampled. This allows for smaller and in many cases fewer biopsies with greater accuracy.

Next it makes it possible to avoid cervical conization in many cases. When the lesion is entirely visualized

TABLE 2

Class II Pap Smears

Pap	No Lesion or Neg. Biopsy	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	Carcinoma in-situ	% Malig.
II−	10	8	10	3	0	0
II	71	94	107	55	20	5.8
II+	3	8	16	20	10	17.5
					TOTAL — All IIs	6.9%

and the diagnosis is established, cryoconization can be done with the confidence that a severe lesion is not being missed. Cervical conization can be reserved to those cases where there is an abnormality of the Pap with no obvious lesion or where the lesion extends into the endocervical canal and is not completely visualized. Conization biopsy also is used to treat carcinoma-in-situ where preservation of fertility is desired. Cryoconization of less severe lesions is desirable since there is less scarring and distortion of the cervix and less chance for cervical incompetency.

Colposcopy also makes it possible to define the limits of lesions. The significance of this is that hysterectomy can be performed on patients with carcinoma-in-situ without a preceding conization biopsy in many cases. This also avoids the need to take a wide vaginal cuff as was previously advocated. Conization biopsies can be tailored to excise the lesion seen. For example, if a lesion is entirely confined to the ectocervix, there is no need to excise a large portion of the endocervical canal. This decreases the risk of cervical injury during the procedure.

Colposcopy also saves money, by allowing total outpatient evaluation and treatment in many cases. The savings obtained by eliminating most cervical conizations and therefore eliminating hospitalization is an obvious advantage in this day of soaring medical costs.

Although colposcopy offers many advantages and in most cases simplifies the evaluation of abnormal Pap smears, several limitations must be recognized. First the reliability of colposcopy depends largely on the experience of the colposcopist. I do not feel that it is mandatory that the colposcopist be able to make an accurate diagnosis on colposcopic observation, but it is essential that the abnormal tissue patterns be recognized so that the most severe abnormality is biopsied. Secondly, there is a certain percentage of cases in which the entire lesion is not visualized. When this occurs it is important that the colposcopic findings not be relied upon and that conization biopsy be used for the most accurate diagnosis. If the limitations of colposcopy are recognized and appropriate precautions taken, the colposcopy is an extremely valuable tool in safely and accurately diagnosing cervical neoplasia.

Suggested Further Reading

Coppleson M: The new colposcopic terminology. J Reprod Med 16:214, 1976.

Feldman MJ, Kent DR, Linzen EM, Goldstein AI: The making of a colposcopist — a safe and sensible approach. J Reprod Med 16:73, 1976.

Stafl A, Mattingly RF: Colposcopic diagnosis of cervical neoplasia. Obstet Gynecol 41:168, 1973.

Townsend DE, Ostersand DR, Mishell DR et al: Abnormal Papanicolaou smears. Amer J Obstet Gynecol 8:429, 1970.

TABLE 3

Comparison of 99 Colposcopic and Conization Biopsies

		Conization biopsies				
		Negative	Mild Dysplasia	Moderate Dysplasia	Severe Dysplasia	Carcinoma-in-situ
Colposcopic biopsies	No lesion seen or neg. Biopsy	0	1	2	2	0
	Mild Dysplasia	1	0	1	0	0
	Moderate Dysplasia	2	2	0	3	3
	Severe Dysplasia	2	0	5	11	8
	Carcinoma-in-situ	0	4	4	9	39

TABLE 4

	Treatments			
	Biopsy Only	Cryoconization	Conization	Hysterectomy
Biopsy negative	20	23	1	3
Mild dysplasia	21	99	1	3
Moderate dysplasia	10	128	8	3
Severe dysplasia	4	87	18	13
Carcinoma in situ or other malig.	3	5	31	39

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PHYSICIANS — Metropolitan Medical Placement offers assistance through our no obligation to the physician placement service. We always have several active listings throughout Minnesota and we specialize in *aggressively* seeking our opportunities to match each physician's individual needs. If you desire confidentiality and professionalism in our search efforts, then we ask you please to contact Mr. Holmes at 612-831-5232.

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(Continued on Page 306)

Dear Fellow Member of Minnesota Medical Association:

THIS YEAR IN ST. PAUL, the MMA Annual Meeting is planned to show you more of the city than the inside of the headquarters hotel, Radisson St. Paul. Twenty-four accredited courses in continuing medical education are offered. In addition to small seminars, lectures and panel discussion courses, there are skills workshops hosted by some of the local hospitals where registrants may use laboratory facilities unavailable in a hotel setting.

IN DEPTH COURSES in basic clinical medicine are designed for all practitioners. You may find it difficult to choose from among the very excellent courses offered so study this course booklet carefully and select *your* curriculum. Each course will provide an opportunity for growth in knowledge, skills and perspective in defined areas of clinical medicine. A detailed syllabus will be provided for enrollees in each course.

THREE SKILLS WORKSHOPS utilizing clinical and laboratory resources of local hospitals have been added to the program this year. Enrollment is very limited and will be accepted on the basis of the postmark of the registration.

THE FORMAT of the meetings has been changed this year. The Scientific Program will run from 8:30 a.m. to 11:30 a.m. and again from 2:00 p.m. to 5:00 p.m. both Thursday and Friday. The two and one-half hours midday can be used to explore the commercial exhibits and the scientific exhibits.

COURSE SELECTION IS IMPORTANT! Early registration is especially critical this year to assure that space is reserved for you in the course of your selection and that instructional material can be prepared in advance for each participant. The program is fully accredited for CME credit (Category I AMA and Prescribed AAFP). Extensive planning and preparation is responsible for the largest scientific program ever offered at the MMA Annual Meeting. The Medical Education Subcommittee on Scientific Assembly invites you to attend and take advantage of this fine selection of courses.

EXHIBITS open on Wednesday evening May 16, 7:00-9:00 p.m. during the Annual Meeting Reception. Complimentary hors d'oeuvres and cash bar are available in the exhibit hall at this time.

WE LOOK FORWARD TO SEEING YOU IN SAINT PAUL.

Sincerely yours,

Stuart Thorson

Scientific Assembly Subcommittee
Stuart Thorson, M.D., Chairman

P.S. The Local Arrangements Committee of Ramsey County Medical Society has planned exceptional social events for our enjoyment. Include them in your Annual Meeting plans. Details are provided in this booklet.

1979 Scientific Program Chart

	Pioneer Suite	Senate Suite	Indian Suite
THURSDAY MAY 17 8:30-11:30 AM	**A** Office Radiography: Taking Good Films Safely *MN Academy of Family Physicians	**B** Upper Respiratory Infection: Common ENT Problems in Childhood *NW Pediatric Society	**C** Dizziness—A Panel Discussion *MN Academy of O & O
2:00-5:00 PM	**H** Personal Health Enhancement—Are You Really Where You Want To Be? *MMA Subcommittee on Scientific Assembly	**I** Psycho-Social Family Problems *NW Pediatric Society	**J** Alcohol, Pills and Recovery *MMA Resource Group on Alcoholism and Other Chemical Dependencies
	Pioneer Suite	Senate Suite	Indian Suite
FRIDAY MAY 18 8:30-11:30 AM	**N** Topics in Neurology-Part I: • Neurologic Assessment of the Unconscious Patient • Cerebral Vascular Disease *MN Society of Neurological Sciences	**O** Office Allergy: • Asthma • Stinging Insect Hypersensitivity *MN Allergy Society	**P** Management of Common Rheumatologic Problems-Part I: Polyarticular Synovitis—Management of Chronic Multiple Swollen Joints *MMA Resource Group on Rheumatic Diseases
2:00-5:00 PM	**U** Topics in Neurology-Part II: • Headache • Seizures—Primary Care *MN Society of Neurological Sciences	**V** Update in Clinical Virology *MMA Subcommittee on Scientific Assembly	**W** Management of Common Rheumatologic Problems-Part II: Regional Rheumatologic Pain Syndromes *MMA Resource Group on Rheumatic Diseases

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Capitol Room	Minnesota West	Minnesota East	Hospital
D Recent Advances in Clinical Nutrition: What Can I Really Believe About Diets? *MN Academy of Family Physicians	**E** Sports Stress and Contact Injuries: Knee and Neck *MN State Orthopedic Society	LUNCHEON	**F** Practical Skills in Surgical Management St. Paul-Ramsey *MN Chapter, Am. College of Surgeons Limit 20
K Recent Advances in Clinical Medicine *MN Academy of Family Physicians	**L** What's New In Common Skin Diseases? *MN Dermatologic Society	BANQUET	**M** Practical Skills in Surgical Management (Repeat a.m.) Limit 20
Capitol Room	Minnesota East	Hospital	Hospital
Q Basic Electrocardiography—The Normal Electrocardiogram, Acute Myocardial Infarction & Common Arrhythmias *MN Society of Internal Medicine	**R** Major Problems in Trauma *MN Chapter, Am. College of Surgeons	**S** Pulmonary Function Testing St. Joseph's *MN Thoracic Society Limit 8	**T** Basic Cardiac Life Support Certification • • • • • • • • • Basic CPR St. Luke's *Minnesota Affiliate, American Heart Association
X Advanced Electrocardiography—Fascicular Blocks, Diagnosis and Treatment of Complicated Arrhythmias, Exercise and Ambulatory Electrocardiography *MN Society of Internal Medicine	**Y** Current Trends in Surgical Management *MN Chapter, Am. College of Surgeons		

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CME

A. Office Radiography: Taking Good Films Safely

Pioneer Suite 3 Credit Hours

Office Radiography is primarily directed to all non-radiologic physicians who have office X-ray. To date there have been few formal CME Radiography experiences available to practicing physicians.

The emphasis of this session is on producing quality office X-rays safely. A practical safety check list and a problem oriented syllabus on X-ray problems will be available and sent to all registered physicians. Upon completion of this session a participating physician will be able to improve both the safety and quality of his/her X-ray practice.

Sponsor: Minnesota Academy of Family Physicians

Course Directors: Larry C. Stetzner, M.D., Minneapolis
Richard K. Simmons, M.D., Minneapolis
John B. Coleman, M.D., St. Paul

Faculty: Alice T. Dolezal, Minneapolis
Dennis Moore, Eden Prairie
Jack Stevens, Niles, Illinois
John B. Coleman, M.D., St. Paul

B. Upper Respiratory Infection: Common ENT Problems in Childhood

Senate Suite 3 Credit Hours

The specific objective of this program will be to acquaint physicians with:

a) Bacteriology of otitis media

b) Indications for tonsillectomy

c) Allergy in infants and children

d) Common problems of immunity

e) Streptococcal throat infections

After attending this course, the physician should have a clear concept of some of the pathophysiologic processes involved in common ENT problems of childhood.

Sponsor: Northwestern Pediatric Society

Course Director: William Krivit, M.D., Ph.D., Minneapolis

Faculty: Scott Giebink, M.D., Minneapolis
Lewis Wannamaker, M.D., Minneapolis
Edward Kaplan, M.D., Minneapolis
Lloyd Fish, M.D., Minneapolis
Paul Quie, M.D., Minneapolis

C. Dizziness—A Panel Discussion

Indian Suite 3 Credit Hours

The symptom complex of dizziness is one that confronts most physicians almost daily in the care of their patients. Dizziness knows no age limits or sex bias, and quite often requires the input of many physicians

continued on next page

before a specific diagnosis is made and therapy instituted. Unfortunately, many cases of dizziness are labeled as "labyrinthitis" or "Meniere's disease" without substantiation, deferring the actual diagnosis and perhaps specific therapy. Even though all physicians see patients with this symptom at one time or another, the three specialties who seem to be primarily consulted regarding this troublesome problem are otolaryngology, neurology and internal medicine or cardiology.

For this reason, the panel will attempt to thrash out the problem as they see it in order to give the participants of this course a lucid and orderly method in which to approach their dizzy patients. There will be ample time at the conclusion of formal presentations for a panel discussion complete with questions and answers. Please try to prepare your questions in advance of the session, if at all possible.

Sponsor: Minnesota Academy of Ophthalmology and Otolaryngology

Course Director: Melvin E. Sigel, M.D., Minneapolis

Faculty: Melvin E. Sigel, M.D., Minneapolis
A. B. Baker, M.D., Ph.D., Minneapolis
H. M. Paisner, M.D., Minneapolis
Robert A. VanTassel, M.D., Minneapolis

D. Recent Advances in Clinical Nutrition: What Can I Really Believe About Diets?

Capitol Room 3 Credit Hours

This course will give participants background information, practical clinical advice, and present day thinking regarding diagnosis and treatment of nutritionally related diseases.

Perhaps no other field of medicine has been so grossly neglected, and yet is so clinically important as that of nutritionally related disease. Obesity, malnutrition, and the plethora of claims in the nutritional field give much emphasis to the fact that primary physicians must increase their knowledge about nutritional diseases. This course will attempt to give clear, practical answers to several of these questions. Ample time has been designated for audience participation and clinical discussions.

Three major areas will be discussed: (1) Basic Clinical Concepts In Nutritionally Related Diseases, (2) The Real Truth About Dietary Treatments "The Mote Versus The Splinter," (3) Ideas For Practical Dietary Treatment And Its Effect On Infection And Cancer.

Sponsor: Minnesota Academy of Family Physicians

Course Director: C. Paul Martin, M.D., Marshall

Faculty: Arnold Anderson, M.D., Minneapolis
C. Wayne Callaway, M.D., Rochester
John Murray, M.D., D.SC., F.R.C.P., Minneapolis

E. Sports Stress and Contact Injuries: Knee and Neck

Minnesota West 3 Credit Hours

A course for general physicians and orthopedists outlining initial care and management of a selection of sports injuries likely to be encountered in a number of common sports activities. Basic mechanisms of sports injuries to the neck and knee will be presented to enable physicians to evaluate and manage these injuries with greater confidence both on the field and afterward.

continued on next page

Sponsor: Minnesota State Orthopedic Society

Course Director: James Kramer, M.D., St. Paul

Faculty: Lowell D. Lutter, M.D., St. Paul
Roby C. Thompson, Jr., M.D., Minneapolis
David R. Olson, M.D., Minneapolis
Donald R. Lannin, M.D., St. Paul
Thomas H. Coplin, R.P.T., St. Paul

F/M. Practical Skills in Surgical Management

St. Paul-Ramsey Hospital 3 Credit Hours

1. Lectures giving the indications for and techniques of diagnostic peritoneal lavage, closed chest thoracostomy, Swan Ganz pulmonary pressure monitoring and intra-aortic counter pulsation support.
2. Dog laboratory experience in diagnostic peritoneal lavage, closed chest thoracostomy, Swan Ganz catheter placement and intra-aortic counter pulsation support.

Sponsor: Minnesota Chapter, American College of Surgeons

Course Director: Lynn D. Solem, M.D., St. Paul

Faculty: Jeffrey B. Howe, Minneapolis
Herbert J. Crandall, St. Paul
Lynn D. Solem, M.D., St. Paul

H. Personal Health Enhancement—Are You Really Where You Want To Be?

Pioneer Suite 3 Credit Hours

To discuss personal health enhancement in three main categories: nutritional health, physical health and mental health in the perspective of the busy practitioner. Subjects will be discussed in the following lively and stimulating presentations:

- MEDICINE & NUTRITION
  Calories, Cholesterol and Chicanery—Does any of it make sense?
- PHYSICAL CONDITIONING AND ITS ROLE IN PERSONAL HEALTH ENHANCEMENT
  Is there anything left for the non-runner?
- CONDITIONING INDUCED JOINT INJURIES—Didn't I tell you you were overdoing it?
- PSYCHOLOGICAL HEALTH—Is your head on right?

The program will address these subjects with the intention of providing the practitioner with guidelines for long term survival.

Sponsor: MMA Subcommittee on Scientific Assembly

Course Directors: John Burns, M.D., St. Paul
James Flinn, M.D., Redwood Falls

Faculty: Robert Olson, M.D., Ph.D., St. Louis, Missouri
John M. Kelly, Ph.D., St. Cloud
Fred Zamberletti, St. Paul
Philip Margolis, M.D., Ann Arbor, Michigan

I. Psycho-Social Family Problems

Senate Suite — 3 Credit Hours

The specific objectives of this program will be to acquaint physicians with techniques and sources for care and management of diverse types of psychiatric problems seen in pediatrics. These include:

a) Sexual problems of teenaged children

b) Incest

c) Single father families

d) Learning and behavior problems in school children

e) Psychological problems relating to death and dying

f) Child abuse

Sponsor: Northwestern Pediatric Society

Course Director: William Krivit, M.D., Ph.D., Minneapolis

Faculty: Daniel Kohen, M.D., Minneapolis
Arthur Jaffe, M.D., Minneapolis
Amos Deinard, M.D., Minneapolis
Pi-Nian Chang, Ph.D., Minneapolis
Elizabeth Jerome, M.D., Minneapolis
Rachel Trockman, M.D., Minneapolis
Joanne Pearson, M.D., Minneapolis

J. Alcohol, Pills and Recovery

Indian Suite — 3 Credit Hours

The new and excellent film ALCOHOL, PILLS AND RECOVERY, produced under the direction of Doctor Joseph A. Pursch, Chief of the Navy Alcohol Rehabilitation Service at the Naval Regional Medical Center in Long Beach, California, will be shown and discussed by Doctor Pursch and a panel of Minnesota physicians involved in chemical dependency programs. General group discussion will be encouraged. The objective of this course is to deepen our understanding of the problems of chemical dependency, particularly alcoholism, and to improve our ability to help patients with such problems.

Sponsor: MMA Resource Group on Alcoholism and Other Chemical Dependencies

Course Director: Robert Bjornson, M.D., St. Paul

Faculty: Joseph A. Pursch, M.D., Long Beach, California
George Mann, M.D., Minneapolis
Thomas Weier, M.D., St. Paul
Joseph Westermeyer, M.D., Minneapolis
George Lundgren, M.D., Shakopee
Robert Bjornson, M.D., St. Paul

K. Recent Advances in Clinical Medicine

Capitol Room 3 Credit Hours

This course will present four clinical areas in medical practice of interest to a primary care audience and provide information applicable to daily office and hospital practice.

- Office Evaluation and Management of Peripheral Arterial and Venous Disease of the Lower Extremities—Participants will be able to recognize pertinent history and physical findings of peripheral vascular disease and obtain appropriate follow-up studies needed for optimal treatment.
- Glycosylated Hemoglobins and Diabetes Mellitus—Participants will be able to recognize potential importance and utilize hemoglobin A1C levels in the management of diabetes mellitus.
- Evaluation and Management of Epiphyseal Injuries—Participants will be able to recognize and effectively treat simple noncomplicated epiphyseal injuries and gain insight into recognizing epiphyseal injuries which are potentially deforming in nature.
- Office Management of a Neck Mass—Participants will be able to properly diagnose and manage the majority of neck lesions in children and adults.

Sponsor: Minnesota Academy of Family Physicians

Course Director: Robert J. Cumming, M.D., St. Cloud

Faculty: James F. DeVinck, M.D., St. Cloud
Hans H. Engman, M.D., St. Cloud
Dwight E. Jaeger, M.D., St. Cloud
Richard A. Schlorf, M.D., St. Cloud

L. What's New in Common Skin Diseases?

Minnesota West 3 Credit Hours

This course is designed for physicians in primary medical practice. Emphasis is placed on diagnosis and therapy (especially recent advances) of dermatologic problems that are currently common. The presentations will utilize 35mm slides, lectures, mini-case presentations and group discussions. Ample time will be allowed for questions and discussions with a panel. Emphasis will be placed upon discussion of acne, fungal infections, common alopecias, scabies, and what's new in topical treatment.

Sponsor: Minnesota Dermatologic Society

Course Director: Milton Orkin, M.D., Minneapolis

Faculty: Milton Orkin, M.D., Minneapolis
Sigfrid Muller, M.D., Rochester
John Strauss, M.D., Iowa City, Iowa
H. Irving Katz, M.D., Fridley
Ken Manick, M.D., Minneapolis

M. Practical Skills in Surgical Management

St. Paul-Ramsey Hospital 3 Credit Hours

Repeat of F

N. Topics in Neurology: Part I
Neurologic Assessment of the Unconscious Patient
Cerebral Vascular Disease

Pioneer Suite	3 Credit Hours

The neurological section is designed to give practical information in areas of neurology that are commonly seen by practicing physicians, particularly in Family Practice, Pediatrics and Internal Medicine. Four areas will be covered, two in the morning, two in the afternoon, leaving time for discussion.

The morning session will begin with a presentation of the neurologic assessment of the unconscious patient. This will be a description of a modified neurologic examination and discussion of appropriate tests to distinguish between such things as intracranial hemorrhage, drug intoxification and metabolic problems.

The second portion of the morning session will be devoted to cerebral vascular disease. Emphasis will be placed on diagnosis of impending stroke and the relative value of various diagnostic procedures. Following that will be a discussion of medical and surgical treatment.

Sponsor: Minnesota Society of Neurological Sciences

Course Director: Donald Erickson, M.D., Minneapolis

Faculty: Myoung Lee, M.D., Minneapolis
Ronald Cranford, M.D., Minneapolis
Donald Erickson, M.D., Minneapolis
Gaylan Rockswold, M.D., Minneapolis

O. Office Allergy: Asthma
Stinging Insect Hypersensitivity

Senate Suite	3 Credit Hours

This course is designed to review the management of two aspects of office allergy: asthma and stinging insect hypersensitivity.

The first part of this course is designed to review recent advances made in the use of medications to afford better control of patients with asthma. Lectures will cover the basic pathophysiology of asthma and the practical use of Theophyllin, B_2 agonists, and inhalational steroids. Participants can expect to become more knowledgeable with the use of these medications in the treatment of patients with asthma.

The second part of this course will cover the significant problem of stinging insect hypersensitivity. The discussion will include the type of reactions that occur, the available methods of diagnosis (skin testing and RAST) and treatment of these patients (acute reactions, prevention, and role of immunotherapy). It is expected, following this discussion, that physicians will know how to evaluate and treat patients who present with this life threatening problem.

Sponsor: Minnesota Allergy Society

Course Director: Edward J. O'Connell, M.D., Rochester

Faculty: Edward J. O'Connell, M.D., Rochester
Stephen C. Weisberg, M.D., Minneapolis
Quinton C. Callies, M.D., Rochester
William F. Schoenwetter, M.D., Minneapolis
John W. Yunginger, M.D., Rochester

P. Management of Common Rheumatologic Problems: Part I
Polyarticular Synovitis—Management of Chronic Multiple Swollen Joints

Indian Suite — 3 Credit Hours

Education for recognition of early active rheumatoid arthritis and appropriate treatment programs, depending upon the course of the disease; and recognition of rheumatoid variants and their clinical significance in relationship to treatment.

Sponsor: MMA Resource Group on Rheumatic Diseases

Course Director: Richard Tompkins, M.D., Rochester

Faculty: Conrad Butwinick, M.D., St. Paul
Roger Colton, M.D., St. Paul
Richard Tompkins, M.D., Rochester

Q. Basic Electrocardiography—The Normal Electrocardiogram, Acute Myocardial Infarction and Common Arrhythmias

Capitol Room — 3 Credit Hours

During the past decade new concepts have emerged in the field of electrocardiography which, when properly utilized, can improve our level of patient care. The purpose of this course is to enable the practicing physician to utilize these newer concepts of electrocardiography as well as to reinforce the utilization of previously learned basic concepts so that the physician may improve the effectiveness and efficiency of patient care.

This course is intended for those who would like to review basic concepts in electrocardiography. The normal electrocardiogram and variations of the normal electrocardiogram will be described. Normal atrioventricular conduction pathways and their alterations in disease states including acute myocardial infarction will be outlined. Electrocardiographic changes during acute myocardial infarction will be demonstrated and compared with electrocardiographic changes in other disease states which may simulate acute myocardial infarction.

Sponsor: Minnesota Society of Internal Medicine

Course Director: Fredarick L. Gobel, M.D., Minneapolis

Faculty: Edward Ryan, M.D., Duluth
Richard Guthrie, M.D., St. Paul
Naip Tuna, M.D., Minneapolis
Kyuhyun Wang, M.D., Minneapolis
Gerald Gau, M.D., Rochester

R. Major Problems in Trauma

Minnesota East — 3 Credit Hours

Lectures to update the current management concepts of colon and rectal injuries, the use of the G-suit in trauma, management regimens of blunt thoracic trauma, and urgent orthopedic injuries. Review of mortality and morbidity resulting from the repeal of the Minnesota Mandatory Motorcycle Helmet Law. Organizational concepts for a rural trauma program. Expert advice on difficult problems of abdominal and thoracic trauma and of hand, orthopedic and plastic surgery problems and of trauma care in the emergency room.

continued on next page

Sponsor: Minnesota Chapter, American College of Surgeons

Course Director: Alan R. Shons, M.D., Ph.D., Minneapolis

Faculty: Earl Yonehiro, M.D., Ph.D., Minneapolis
David Rothenberger, M.D., St. Paul
Ernest Ruiz, M.D., Minneapolis
Robert Maxwell, M.D., Minneapolis
Lynn Solem, M.D., St. Paul
Edward Novak, St. Paul
Daniel Gaither, M.D., St. Paul
C. Thomas Thompson, M.D., Tulsa, Oklahoma
David McAfee, M.D., Willmar
Robert van Tyn, M.D., St. Paul
Alan R. Shons, M.D., Ph.D., Minneapolis

S. Pulmonary Function Testing

St. Joseph's Hospital, St. Paul — 3 Credit Hours

The course will consist of a three hour period of discussion and demonstration of basic measurements of pulmonary function. Course participants will have an opportunity to learn how to perform the tests and how to interpret the results. Emphasis will be on those tests appropriate for physicians' offices and community hospitals. These will include the measurement of forced vital capacity, maximal expiratory flow-volume curves, closing volumes, and arterial blood gas analysis. The course is limited to eight participants and will be held at the Pulmonary Function Laboratory of St. Joseph's Hospital in St. Paul.

Sponsor: Minnesota Thoracic Society

Course Director: Thomas F. Mulrooney, M.D., St. Paul

Faculty: William Sallberg, R.R.T., St. Paul
Bradford Anderson, B.S., St. Paul
Thomas F. Mulrooney, M.D., St. Paul

T. Basic Cardiac Life Support Certification

United Hospitals, St. Luke's Division — 6 Credit Hours

Basic Cardiac Life Support includes the following four areas: unwitnessed cardiac arrest, witnessed cardiac arrest, opening an obstructed airway, infant resuscitation. Initial Basic Rescuer certification is based on a passing grade on the cognitive test and perfection in the performance examination for an unwitnessed cardiac arrest in an adult. If time permits, participants may also take the performance examinations for witnessed cardiac arrest, opening an obstructed airway and infant resuscitation. Participants will have an opportunity for manikin practice prior to the actual certification performance. Attendance will be limited.

Sponsor: Minnesota Affiliate, American Heart Association

Course Director: Victor Tschida, M.D., St. Paul

continued on next page

U. Topics in Neurology: Part II
Headache
Seizures—Primary Care

Pioneer Suite 3 Credit Hours

The neurological section is designed to give practical information in areas of neurology that are commonly seen by practicing physicians, particularly in Family Practice, Pediatrics and Internal Medicine. Four areas will be covered, two in the morning, two in the afternoon, leaving time for discussion.

The first afternoon session will be devoted to diagnosis and treatment of the common headache problem. The second portion will be devoted to diagnosis and treatment of non-complex seizure disorders. Emphasis will be placed on the first line of treatment and the basic diagnostic testing for childhood and adult seizures.

Sponsor: Minnesota Society of Neurological Sciences

Course Director: Donald L. Erickson, M.D., Minneapolis

Faculty: Terrance D. Capistrant, M.D., St. Paul
Robert L. Kriel, M.D., St. Paul
Robert J. Gumnit, M.D., St. Paul

V. Update in Clinical Virology

Senate Suite 3 Credit Hours

This course is designed to bring the practitioner up to date in several rapidly advancing areas of clinical virology in order to enhance his utilization of the diagnostic virology laboratory and to provide an overview of currently recommended practices for prevention and treatment of viral infections.

Subjects to be covered are:

1. Rapid diagnostic techniques for recognition of respiratory and central nervous system viral illnesses.
2. Prevention, diagnosis, and management of viral hepatitis.
3. Immunizations for viral diseases: new recommendations for measles and rubella and information on vaccines being developed for cytomegalovirus and varicella zoster.
4. Toward effective treatment of viral infections: amantadine, isoprinosine, adenine arabinoside, interferon and its inducers and beyond.

Sponsor: MMA Subcommittee on Scientific Assembly

Course Director: Henry H. Balfour, Jr., M.D., Minneapolis

Faculty: Henry H. Balfour, Jr., M.D., Minneapolis
Gilbert M. Schiff, M.D., Cincinnati, Ohio

W. Management of Common Rheumatologic Problems: Part II
Regional Rheumatologic Pain Syndromes

Indian Suite 3 Credit Hours

Education for recognition of common geographic pain syndromes in the shoulders, hands, and feet with basic diagnostic and therapeutic endeavors appropriate to these regions.

continued on next page

Sponsor: MMA Resource Group on Rheumatic Diseases

Course Director: Roger S. Colton, M.D., St. Paul

Faculty: Robert Cofield, M.D., Rochester
Chris Tountas, M.D., St. Paul

X. Advanced Electrocardiography—Fascicular Blocks, Diagnosis and Treatment of Complicated Arrhythmias, Exercise and Ambulatory Electrocardiography

Capitol Room 3 Credit Hours

During the past decade new concepts have emerged in the field of electrocardiography which, when properly utilized, can improve our level of patient care. The purpose of this course is to enable the practicing physician to utilize these newer concepts of electrocardiography as well as to reinforce the utilization of previously learned basic concepts so that the physician may improve the effectiveness and efficiency of patient care. This will supplement Course Q.

This course is intended for those who have completed Basic Electrocardiography and would like to continue, as well as for those internists, family physicians, anesthesiologists and others who find it necessary to interpret electrocardiograms each day. This course will emphasize recognition and management of supraventricular and ventricular arrhythmias as well as electrocardiographic stress testing and ambulatory electrocardiographic monitoring.

Sponsor: Minnesota Society of Internal Medicine

Course Director: Fredarick L. Gobel, M.D., Minneapolis

Faculty: Edward Ryan, M.D., Duluth
Richard Guthrie, M.D., St. Paul
Naip Tuna, M.D., Minneapolis
Kyuhyun Wang, M.D., Minneapolis
Gerald Gau, M.D., Rochester

Y. Current Trends in Surgical Management

Minnesota East 3 Credit Hours

Review of current status of selected surgical procedures and techniques (coronary bypass surgery, diagnostic laparoscopy, breast reconstruction and femoral profundoplasty). Expert advice on difficult problems involving cardiovascular surgery, infections, burns and OB/GYN.

Sponsor: Minnesota Chapter, American College of Surgeons

Course Director: Alan R. Shons, M.D., Ph.D., Minneapolis

Faculty: Robert Anderson, M.D., Minneapolis
Francisco Puga, M.D., Rochester
Demetre M. Nicoloff, M.D., Ph.D., Minneapolis
Joseph J. Garamella, M.D., Ph.D., Minneapolis
J. E. Wall, M.D., Duluth
Alan R. Shons, M.D., Ph.D., Minneapolis
Peter Pairolero, M.D., Rochester
Ronald H. Dietzman, M.D., Ph.D., St. Paul
Richard Strate, M.D., St. Paul

SCHEDULE OF EVENTS

Wednesday May 16

8:00 am	Golf Tournament	White Bear Yacht Club
9:00 am	Tennis Tournament	Lilydale Tennis Club
	Footraces	Harriet Island Park (Assemble at Radisson)
1:00 pm	House of Delegates	Radisson
2:00 pm	General Registration	Radisson
3:45 pm	Reference Committees	Radisson
5:00 pm	Auxiliary Registration	Radisson
6:00 pm	The New Wizard Oil Troupe "A Medicine Show"	Radisson
7:00 pm	Annual Meeting Reception and Exhibit Opening	Radisson

Thursday May 17

7:00 am	General Registration	Radisson
7:00 am	Breakfast Meetings	Radisson St. Paul Athletic Club
8:00 am	Exhibits	Radisson
8:00 am	Auxiliary Registration and Continental Breakfast	Radisson
8:30 am	Scientific Program	Radisson St. Paul-Ramsey Hospital
9:00 am	Auxiliary Pre-Convention Meeting	Radisson
11:00 am	Auxiliary City Tour of St. Paul	Departs from Radisson
12:00 noon	Luncheon "Why Don't They Tell the Truth About Old Age?" George Sheehan, MD	Radisson
2:00 pm	Scientific Program	Radisson St. Paul-Ramsey Hospital
3:00 pm	MINNPAC Annual Meeting	Radisson
6:00 pm	President's Reception	Radisson
7:00 pm	Banquet	Radisson

Friday May 18

7:00 am	General Registration	Radisson
7:00 am	Breakfast Meetings	Radisson
8:00 am	Exhibits	Radisson
8:00 am	Auxiliary Registration and Continental Breakfast	Minnesota Club
8:30 am	Scientific Program	Radisson St. Luke's Hospital St. Joseph's Hospital
9:00 am	Auxiliary Annual Meeting	Minnesota Club
12:00 noon	Luncheon Meetings:	
	Minnesota Chapter, American College of Emergency Physicians	Radisson
	Minnesota Chapter, American College of Surgeons	St. Paul Athletic Club
12:30 pm	Auxiliary Annual Luncheon	Minnesota Club
1:00 pm	House of Delegates	St. Paul Athletic Club
2:00 pm	Scientific Program	Radisson St. Luke's Hospital
6:00 pm	Minnesota Academy of Ophthalmology & Otolaryngology	Arts & Science Center

Saturday May 19

9:00 am	Minnesota Medical Alumni Society Spring Seminar	University of Minnesota
	Minnesota Society of Internal Medicine	Northwestern Hospital

NAME____ (Please Print)

ADDRESS____
Street

____
City State Zip

Specialty________________ (Specify) Resident______ Medical Student______ Other __________

1979 Minnesota Medical Association Scientific Program Registration

CME Registration Fee: $25 for MMA Members
$50 for Non-Members
Exempt—Residents and Medical Students

Please make check payable to Minnesota Medical Association.

The scientific program is comprised of twenty-four courses. When registering, please pay attention to the time element of each course. On each day you have a choice of attending a morning and afternoon course or CPR, an all day course on Friday. Indicate, by number, your 1st, 2nd and 3rd choices for EACH TIME PERIOD. You will receive confirmation of your choices. NO ADVANCE REGISTRATION CAN BE ACCEPTED AFTER MAY 4.
Please pick up your registration materials at the registration desk in the Radisson St. Paul Hotel.

CME MAY 17-18, 1979 CME

THURSDAY, MAY 17

Morning Courses—8:30-11:30 AM

A.____ Office Radiography: Taking Good Films Safely

B.____ Upper Respiratory Infection: Common ENT Problems In Childhood

C.____ Dizziness—A Panel Discussion

D.____ Recent Advances In Clinical Nutrition: What Can I Really Believe About Diets?

E.____ Sports Stress and Contact Injuries: Knee and Neck

F.____ Practical Skills In Surgical Management (Limit 20)

Afternoon Courses—2:00-5:00 PM

H.____ Personal Health Enhancement—Are You Really Where You Want To Be?

I.____ Psycho-Social Family Problems

J.____ Alcohol, Pills And Recovery

K.____ Recent Advances In Clinical Medicine

L.____ What's New In Common Skin Diseases?

M.____ Practical Skills In Surgical Management (repeat) (Limit 20)

MMA Requests Authorization To Release Information Of Your Attendance During This Meeting:
Yes____ No____

DETACH THIS FORM AND SEND WITH CHECK TO:

Minnesota Medical Association
'79 Annual Meeting
101 East Fifth Street—#900
St. Paul, Minnesota 55101

FRIDAY, MAY 18

Morning Courses—8:30-11:30 AM

N.____ Topics In Neurology: Part I—Neurologic Assessment Of The Unconscious Patient; Cerebral Vascular Disease

O.____ Office Allergy: Asthma—Stinging Insect Hypersensitivity

P.____ Management Of Common Rheumatologic Problems: Part I—Polyarticular Synovitis: Management Of Chronic Multiple Swollen Joints

Q.____ Basic Electrocardiography—The Normal Electrocardiogram, Acute Myocardial Infarction And Common Arrhythmias

R.____ Major Problems In Trauma

S.____ Pulmonary Function Testing (Limit 8)

All Day Course Beginning at 8:30 AM

T.____ Basic Cardiac Life Support Certification

Afternoon Courses—2:00-5:00 PM

U.____ Topics In Neurology: Part II—Headache; Seizures—Primary Care

V.____ Update In Clinical Virology

W.____ Management Of Common Rheumatologic Problems: Part II—Regional Rheumatologic Pain Syndromes

X.____ Advanced Electrocardiography—Fascicular Blocks, Diagnosis and Treatment of Complicated Arrhythmias, Exercise And Ambulatory Electrocardiography

Y.____ Current Trends In Surgical Management

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Special accommodation request: ______________________________

ARRIVAL: Date________Time________ DEPARTURE: Date________Time________

Guarantee late arrival? Yes________ No________

You will receive a confirmation directly from the hotel. Rooms are held until 6:00 P.M. unless request for late arrival. *Please do not include the payment of your reservation with this form!*

Detach this form and send to: MINNESOTA MEDICAL ASSOCIATION
'79 Annual Meeting
101 East Fifth Street—#900
St. Paul, MN 55101

MEAL TICKET RESERVATIONS—MMA ANNUAL MEETING
May 16-17-18, 1979 • Radisson St. Paul Hotel

TICKETS WILL BE MAILED TO YOU.

Name______________________________

Address______________________________

City________________ State____________ Zip________

Please make checks payable to Minnesota Medical Association and return check with this card to:
MINNESOTA MEDICAL ASSOCIATION
'79 Annual Meeting
101 East Fifth Street—#900
St. Paul, Minnesota 55101

No ticket sales can be made or refunds granted after May 4. Additional tickets will be on sale at the Annual Meeting Registration Desk beginning May 16.

LUNCHEON • Thursday, May 17, 12:00 noon, Minnesota East Ballroom
$10.00 each Number of Tickets________

PRESIDENT'S RECEPTION/BANQUET • Thursday, May 17, 6:00 pm, Minnesota Ballroom
$18.50 each Number of Tickets________

ANNUAL MEETING RECEPTION • Wednesday May 16, 7-9 pm, Wabasha Hall
Complimentary hors d'oeuvres and cash bar.
Number attending: Self________ Spouse________

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epac Papaverine	150 mg.	3.95	**$6.37**	61.7%
uanil Tablets*	400 mg.	8.15		
epac Meprobamate	400 mg.	1.85	**6.30**	77.3%
rium Capsules*	10 mg.	8.76		
epac Chlordiaze- oxide HCl.	10 mg.	3.90	**4.86**	55.4%

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Classified Advertisements

(Continued from page 286)

OBSTETRICIAN-GYNECOLOGIST, to join 11 member primary care group. 7 Family Physicians, 2 Internists and 2 General Surgeons. Large patient population, newly remodeled and expanded Clinic facility approximately 6 blocks from modern, well equipped 99 bed hospital. Rural community 45 minutes South of the Metro area on 35W. Salary guarantee first year. For more information please contact: Darral Mischke, Clinic Administrator, Faribault Clinic, Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

WANTED: PSYCHIATRIST for Mental Health Center and/or private practice Northwest corner of state. Center desires additional psychiatrist in area. Will either guarantee development of private practice, or full time position with the Center of combination. Excellent salary and fringe benefits. Delightful professional staff developing innovative programs in the seven county area. A professionally exciting opportunity. Contact Roy Waters, Executive Director, Northwestern Mental Health Center, College Avenue, Crookston, MN 56716. Phone: area code (218) 281-3940

INTERNIST AND FAMILY PHYSICIANS wanted by 10 person medical group in Alexandria, Minnesota. Please contact Paul H. Engebretson, M.D., 610 Fillmore, Alexandria, MN 56308. Telephone: (AC612) 763-5123"

ENT, OPTHALAMOLOGY, FAMILY PRACTICE and CARDIOLOGY specialty positions available with Mankato Clinic, Ltd. Our 30 man multi-specialty group attracts specialty referrals from a Southern Minnesota area of 200,000 population. Excellent group practice opportunity in All-American community with full hospital services; full range of group fringe benefits; liberal time off; salary first year; incentive pay thereafter. For more information call collect R. F. Roskens, Administrator, or Dr. B. C. McGregor, 507-625-1811.

WANTED: Orthopedic surgeon, Board Certified or eligible to join nine man group consisting of 8 family practitioners and general surgeon in University town with trade area population of 22,000, 30 miles southeast of St. Paul, MN JCAH approved hospital. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, Ltd., River Falls, WI 54022, or call collect (715) 425-6701.

NATIONWIDE AND EUROPE — Army seeking physicians to age 57. Salary from $30,000 depending on qualifications and experience. Choose your location. Relocation cost paid. 30 days paid vacation, no malpractice premium, excellent benefits. Type of practice, location, salary and rank guaranteed prior to two year obligation. GME available. CPT David James, US Army Medical Department, 180 E. Kellogg Blvd, Room 1526, St. Paul, MN 55101, (612) 221-9011. (Call collect).

ORTHOPEDIST DESIRED by 22 man multi-specialty clinic for growing practice in Minneapolis area. Board eligible or board certified desired. Excellent salary and fringe benefits available. Contact Mr. T. Signorelli, 3620 Central Avenue N.E., Minneapolis, MN 55418.

WANTED—F.P./G.P. INTERNIST for large General Practice in South Central Minneapolis. Salary, association & take over in view, exceptional opportunity for F.P. graduate or experienced GP. Write Minnesota Medicine, 542 — 101 E. 5th St. #900, St. Paul 55101 or call collect 612-827-4743.

FAMILY PHYSICIAN to join two Board-Certified family doctors, one physicians assistant, and one family counselor in a young and growing medical practice in beautiful Central Minnesota. The practice is oriented towards holistic medicine with a commitment to patient and community education. 80 minutes to downtown Minneapolis. Cultural and recreational activities in abundance. Salary range $35-43,000 depending on qualifications. Contact Adm. James G. Lawson or Thomas J. Newton, M.D. at Gold Spring Medical Clinic, 26 N. Red River Ave., Cold Spring, Mn., 56320 — 612-685-8641.

WANTED: Board certified or board eligible Internist, General, or with subspecialty. Univ. Comm. of 40,000 with drawing area of about 100,000. One hour from ocean, mountains, or desert. Six months guarenteed income. J.A.C.H. approved Hosp., lic. for 195 beds. Resume to: Box 1506, Loma Linda, Ca. 92354.

WANTED OTOLARYNGOLOGIST to join 22 man multi-specialty clinic in Minneapolis area. Excellent opportunity in a growing practice area and new 350-bed hospital. Contact Mr. T. Signorelli, 3620 Central Avenue N.E., Minneapolis, MN 55418.

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STATE MEDICAL CONSULTANTS SOUGHT — The Minnesota Department of Health (MDH) is requesting applications from qualified physicians for consultation to several agency programs. All positions would be held by contract, and interested physicians will be required to submit formal proposals according to the procedures required by the Minnesota Department of Administration. Information about these procedures is available from the MDH staff members listed in the position notices that follow. Maximum contract amounts and hourly rates will be discussed in the "request for proposals" (RFPs) issued by MDH for each of the described positions.

EMERGENCY MEDICAL SERVICES (EMS): The EMS section is seeking a Medical Director for duties beginning no later than September 1, 1979, to (1) provide continuous advice for its efforts to develop EMS systems in eight regions of Minnesota; (2) draft rules and guidelines for the effective operation of basic and advance life support services, free-standing EMS facilities, and other EMS facilities; (3) plan improvements in such state-wide services as helicopter and fixed-wing life support transportation, poison treatment networks and similarly identified networks of specialized centers for care of the critically ill or injured emergency patients; (4) provide general advice and assistance in efforts to improve initial and continuing educational opportunities for physicians, nurses, and other EMS personnel; and (5) chair the Minnesota EMS Advisory Task Force and other appropriate advisory committees of the EMS section.

Applicants should be actively practicing emergency medicine or a related specialty, be licensed or capable of licensure in Minnesota, have a demonstrated ability for spoken and written communications, and be willing to provide a minimum of the equivalent of one day a week in performing the duties of medical director. Some out-of-state travel and considerable travel in Minnesota will be required. Interested physicians may inquire by telephone or letter to:

Jim Parker
Assistant Chief
EMS Section
Minnesota Department of Health
717 Delaware S.E.
Minneapolis, 55440
(612) 296-5281

A copy of the request for proposal for this contract will be forwarded to potential applicants. The deadline for applications is 4:00 P.M., June 30, 1979.

LONG-TERM CARE MEDICAL CONSULTANT: The Quality Assurance and Review Program is seeking a physician to provide continuous medical guidance on assessment of the quality of care provided to Medicaid patients in long-term care facilities. The physician must have experience in the area of long-term care quality assurance. Consulting services are needed an average of 18 hours per week throughout the year in the Minneapolis office of MDH. The deadline for submission of applications is 4 P.M., May 31, 1979. To obtain a copy of the Request for Proposal for Professional Services, contact:

Kent E. Peterson, Chief
Planning and Resources
Control Section
Minnesota Department of Health
717 S.E. Delaware Street
Minneapolis, Minnesota 55440

LONG-TERM CARE REVIEW: Consulting services by at least nine physicians are sought for medical reviews conducted by the Quality Assurance and Review Program. The Program assesses the quality, quantity and appropriate level of care of Medicaid patients in long-term care facilities in Minnesota. Physician's services are needed in long-term care facilities between 2 to 4 days per month and are scheduled throughout the year. Medical review teams operate in nine regions of the State. Travel by each review physician is generally limited to the multi-county region surrounding MDH District offices. The deadline for submission of applications is 4:00 P.M., May 31, 1979. To obtain a copy of the Request for Professional Services, contact Kent E. Peterson at the address given above.

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(Continued to Page 308)

(Continued from Page 307)

TWENTY-TWO MAN multi-specialty clinic in Minneapolis area desires additional OB-GYN doctor for expanding OB-GYN practice. Excellent salary and fringe benefits. Must be board certified or board eligible. Contact Mr. T. Signorelli, 3620 Central Avenue N.E., Minneapolis, MN 55418.

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dic reassessment of therapy recommended.
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use of increased risk of congenital malformations as
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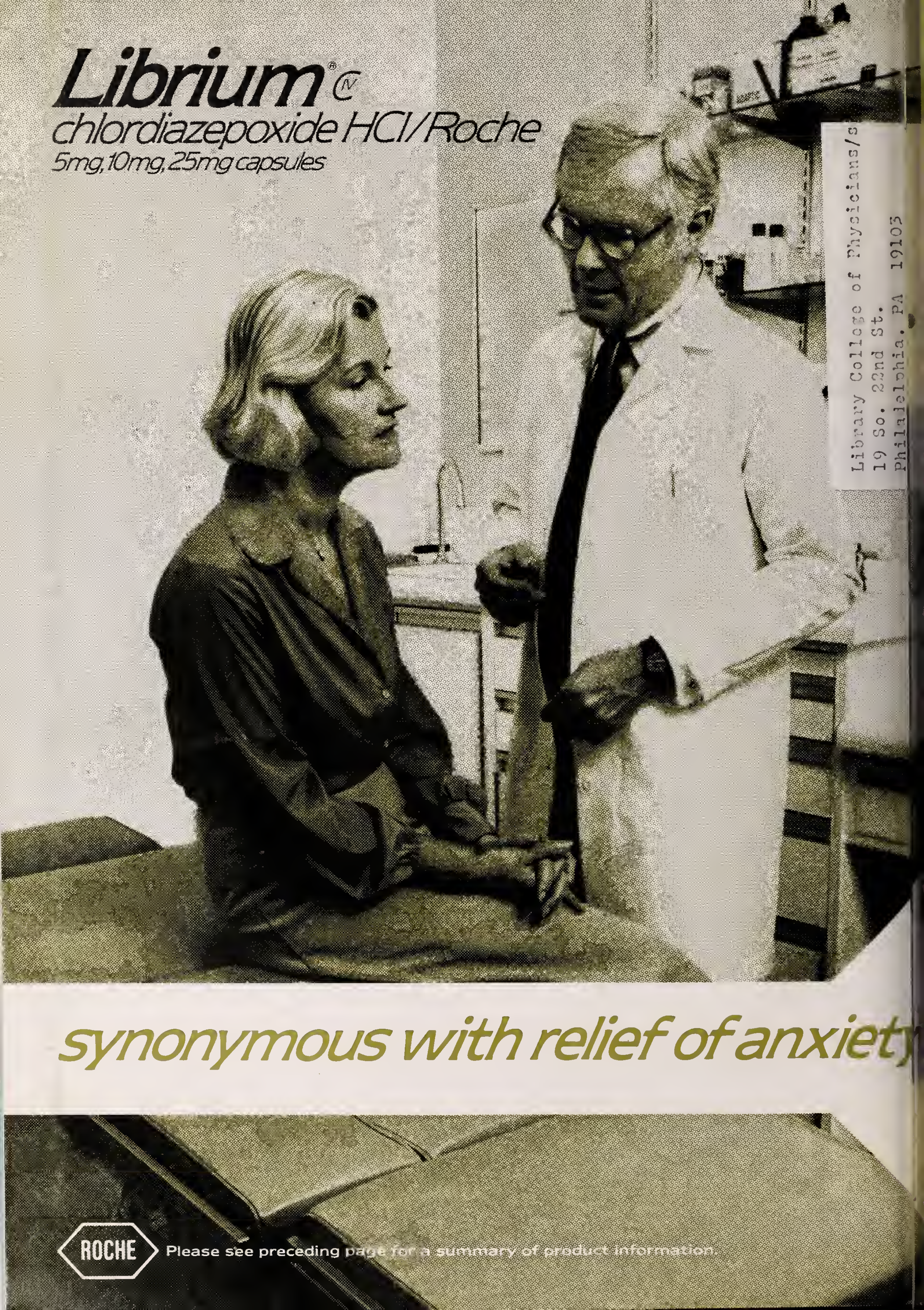

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May 1979

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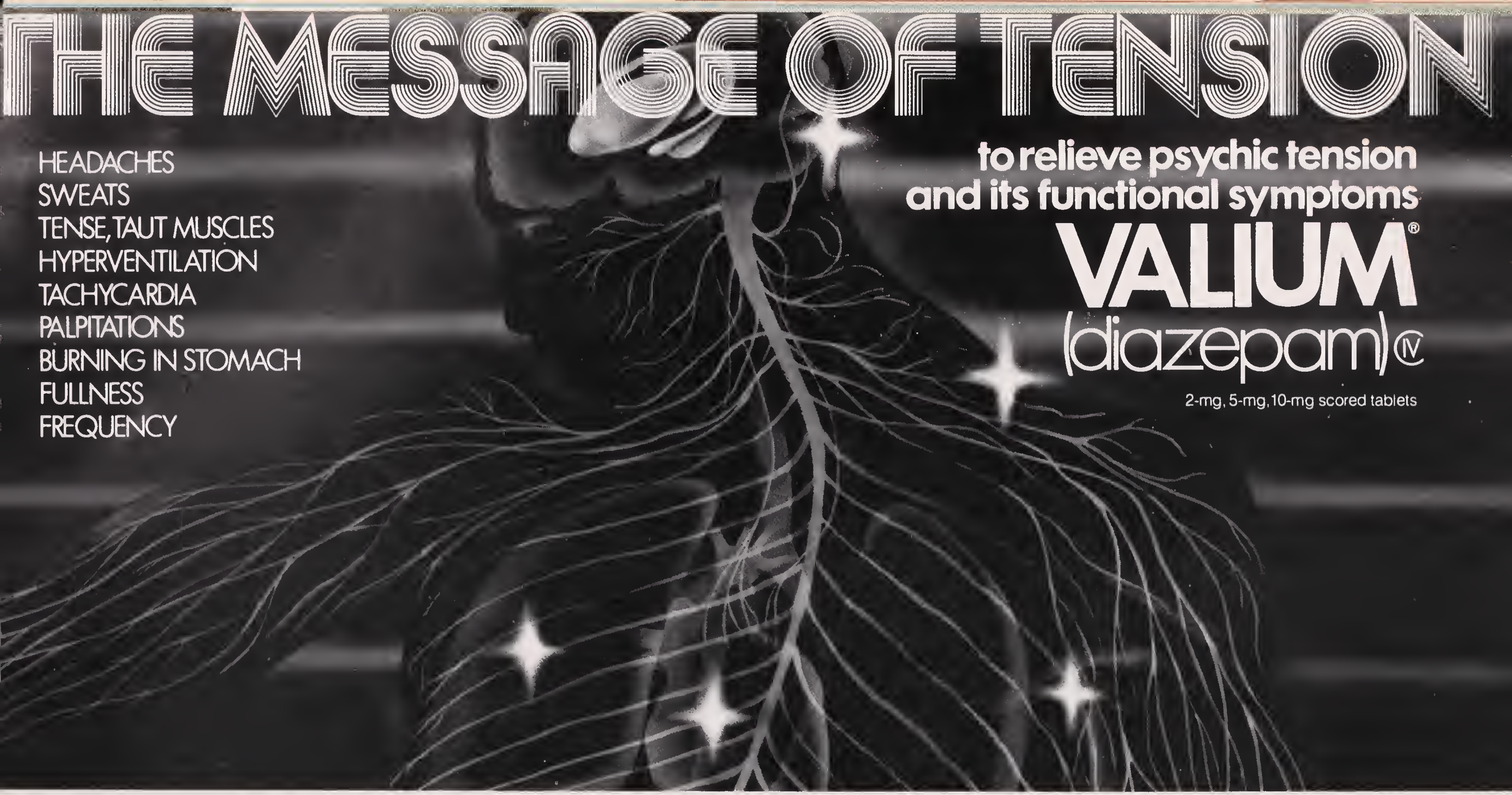

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The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should period-

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or over-

hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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Contents — May, 1979

COVER PHOTOGRAPH — "Gooseberry Falls"
John E. Lonstein, M.D. 316

PRESIDENT'S LETTER — The Presidency
Robert S. Flom, M.D.
President, Minnesota Medical Association 313

HEALTH CARE COST COMMISSION
Richard J. Frey, M.D.
Chairman, Commission on Health Care Costs 315

EDITOR'S NOTEBOOK — Editor's Report to the House of Delegates
Richard L. Reece, M.D.
Editor-in-Chief 317

ORIGINAL CONTRIBUTIONS
Intestinal Fistula from a Toothpick
Peter A. Jernigan, M.D. and Gerald T. Mullin, Jr., M.D. 321
Surgical Treatment of Uremic Pericarditis
David S. Hodge, M.D. et al. 323
Cerebral Tuberculoma
John R. Mawk, M.D. et al. 331

EDITORIALS
Malignancy of the Ovary — *Konald Prem, M.D.* 335
Intestinal Fistula from a Toothpick — *Harrison H. Farley, M.D.* 337
Phenylbutazone-Induced Hepatitis — *Joseph M. Tombers, M.D.* 337

MINNESOTA MEDICINE'S BEST OF THE YEAR 339

FIFTY YEARS OF FAITHFUL SERVICE 341

MINNESOTA MEDICAL ASSOCIATION — Report of Nominating Committee 343

CASE REPORT — Phenylbutazone-Induced Hepatitis
Thomas R. Mayer, M.D. 349

FRACTURE CONFERENCE — Injuries of the Lower Cervical Spine
Miguel E. Cabanela, M.D. and Kenneth A. Johnson, M.D. 351

RHEUMATOLOGY CORNER — Role of Physical Medicine and Rehabilitation in the Care of Rheumatoid Arthritic Patients
Mehrsheed Sinaki, M.D. 358

REVIEW — Malignancy of the Ovary
R. J. Campaigne, M.D. 360

LEGISLATION — Minnesota "Brain Death" Legislation: A Step Forward or Backward? Part II Defining "Brain Death"
John S. Hamlon, M.A. and John M. Burns, M.D 363

HISTORY — Infanticide — A Historical Perspective
Beverly A. Montag, B.S. and Thomas W. Montag, M.D. 368

SPECIAL ARTICLE — Preschool Screening: Right or Ritual?
John F. Hick, M.D. 373

CONTINUING MEDICAL EDUCATION 314, 316, 317, 322, 350, 359, 372, 380

CLASSIFIED ADVERTISEMENT 381

INDEX TO ADVERTISERS 384

Volume 62:5
Pages 309-384

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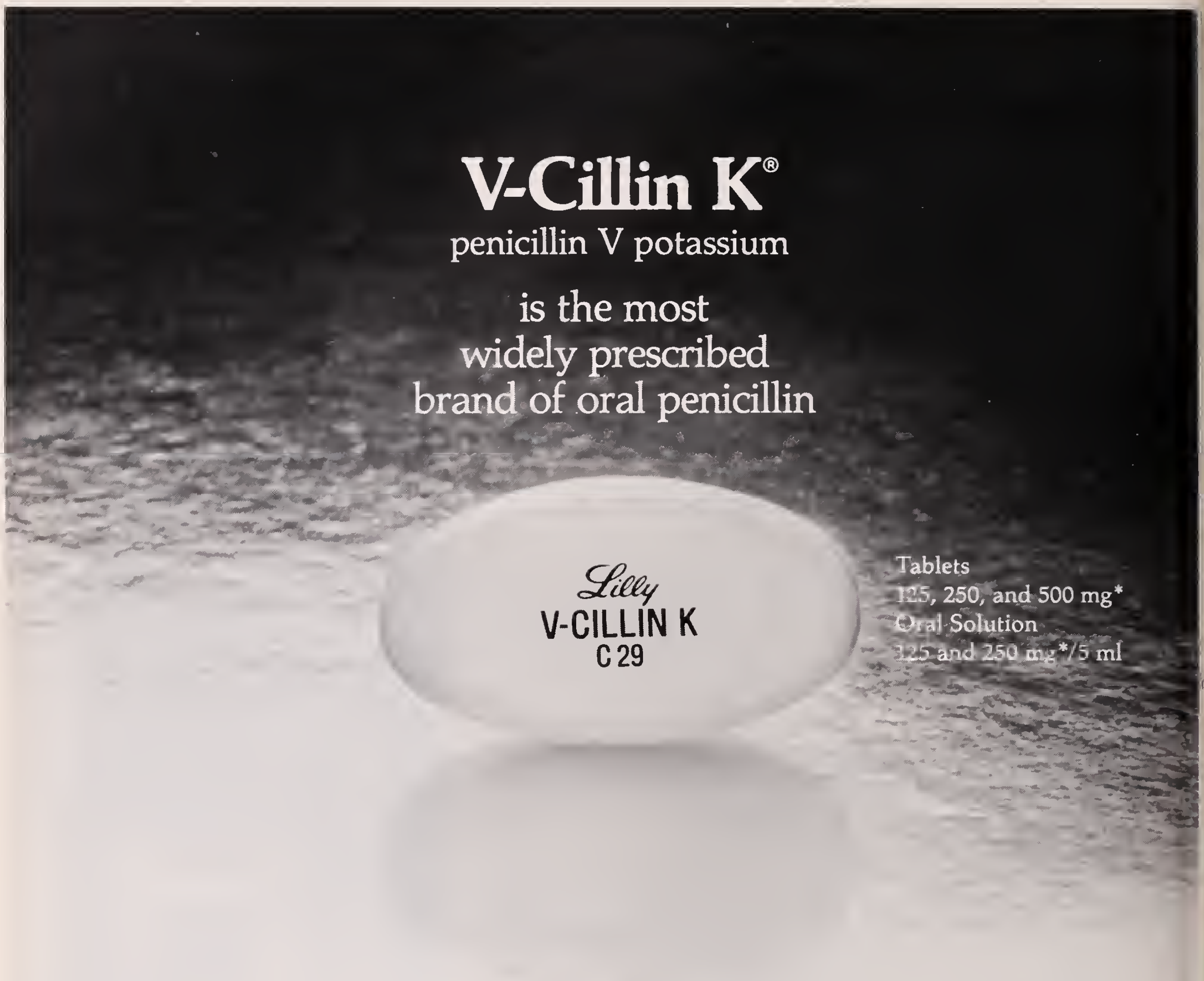

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Contraindication: Previous hypersensitivity to penicillin.

Warnings: Serious, occasionally fatal, anaphylactoid reactions have been reported. Some patients with penicillin hypersensitivity have had severe reactions to a cephalosporin; inquire about penicillin, cephalosporin, or other allergies before treatment. If an allergic reaction occurs, discontinue the drug and treat with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. [102175]

***Equivalent to penicillin V.**

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President's Letter

The Presidency

Having nearly completed the one year tenure of this office it is time to reminisce a bit and to express some general observations.

The office of President is fun. It is fun, because it entails the ceremonial and symbolic representation of the group which I respect and admire the most, the Physicians of Minnesota. This representation takes the form of interfacing with the public, with government, with allied health professions, colleagues in surrounding states, with the AMA and with component specialty societies, and most importantly with the county medical societies and individual members. The office of President is demanding, because it demands enormous amounts of time in the meetings of the Trustees, the Councils of the Medical Association, and the Committee structure. The office of the President is sometimes lonely when all of the real or imagined problems of medicine are dropped at your door step by the public, government, and individual members not to mention the media. Somehow one gets the feeling that everything that has gone wrong, both in and outside of medicine's house, either now or in all preceding history must truly be the fault and responsibility of the President. The bottom line, however, shows a clear positive balance because of the work we do and the talented and dedicated people composing the profession and of the individuals we serve.

The past year has seen intense activity in the area of cost containment and the public document produced by the Health Care Cost Commission is included in this issue. This month the House of Delegates will decide what policies the MMA shall adopt as the result of recommendations made by this free standing Commission.

Considerable effort was extended during this year in establishing liaison and providing input to the various commissioners of departments of state government. Along with the ongoing communication with the Department of Health, considerable time was spent negotiating with the Department of Public Welfare relative to physician reimbursement, as well as surveillance and utilization review programs. While we did not accomplish all that some would have liked to have seen us do, we nonetheless feel that considerable progress was made in this area during the past year.

Effort has been extended in the professional liability insurance area and in the past year a contract was signed between the insurance carrier, a consulting firm, and MMA which has resulted in increased risk prevention activity, claims review, underwriting and actuarial studies. This effort continues and must of necessity be an ongoing program in some form.

Much time and effort has been spent in the area of planning and interfacing with bureaus and agencies of the government created for the purpose of planning but which sometimes goes over into implementation and regulation.

Intense efforts continue as they have in the past with the Legislature. It seems that the attitude of the public and state government is to take a more reasoned and deliberate approach to new legislation.

Continuing Medical Education, as well as Public Health Education remains, of course, one of our major efforts and is, in fact, the basic reason for our existence.

Efforts have been increasing and must continue in the future to make studies and recommendations as to the effects of the environment on man's health.

Lastly but not leastly, the area of services to members is receiving increasing attention by the organization, and the efforts are being stepped up to involve those physicians who are not yet actively participating in the joint efforts of what is known as "organized medicine."

Medicine faces some serious challenges, both in the short and the long range prospect. We live in an era when this country has reached a plateau in its expansion and productivity; and it is in fact stated that we now are ranked seventh in productivity. We live in an era where medical technology stands high in the rate of growth as in industry. We live in an era where consumerism also ranks high as a growth industry. As it spins-off, some signs appear of a trend towards deregulation by government, and hope for some long range deceleration in the rate of growth of that champion of all growth industries, government by bureaus.

I have been pleased to see the awakening of the realization that the physician community may no longer concern itself only with the effort for scientific excellence. Ever increasing numbers are involving themselves in attempts to solve the problems which face society as a whole. So long as we keep our time honored objectives in clear focus, adapt ourselves to the changing needs and desires of the public and continue our scientific studies, the future of this profession cannot be so dismal as some pessimists predict.

Now that I have defined some of the problems it is time for me to welcome the incoming President, Dr. Frank Johnson. It is reassuring to know that the presidency will pass to such a capable individual. I wish you good luck, Frank. I know your judgments will be well thought out, and since I have defined the problems, all that is left for you to do is to solve them.

Robert S. Flom

Robert S. Flom, M.D.
President
Minnesota Medical Association

MMA Annual Meeting

Management of Common Rheumatologic Problems
Friday, May 18, Radisson St. Paul

Part I: Polyarticular Synovitis — Management of Chronic Multiple Swollen Joints

3 credit hours Category I / Prescribed 8:30-11:30 am

Education for recognition of early active rheumatoid arthritis and appropriate treatment programs, depending upon the course of the disease; and recognition of rheumatoid variants and their clinical significance in relationship to treatment.

Part II: Regional Rheumatologic Pain Syndromes

3 credit hours Category I / Prescribed 2:00-5:00 pm

Education for recognition of common geographic pain syndromes in the shoulders, hands and feet with basic diagnostic and therapeutic endeavors appropriate to these regions.

Sponsor: MMA Resource Group on Rheumatic Diseases

Current Trends in Surgical Management
3 credit hours Category I / Prescribed
Friday, May 18, 2:00-5:00 pm, Radisson St. Paul

Review of current status of selected surgical procedures and techniques (coronary bypass surgery, diagnostic laparoscopy, breast reconstruction and femoral profundoplasty). Expert advice on difficult problems involving cardiovascular surgery, infections, burns and OB/GYN.

Sponsor: Minnesota Chapter, American College of Surgeons

Health Care Cost Commission

Commission on Health Care Costs

Recognizing the impact of the unacceptable rate of increase in the cost of health care, the Board of Trustees of the MMA initiated a broad and independent commission charged with the task of identifying major causes of the escalating costs and recommending a remedial course of action. This 21-person commission, representing business and industry, labor, government, communications, insurance carriers, hospital administration, health planning, and physicians, began its deliberation in May, 1977 and released its report in March of this year.

At the onset of this project, it was clearly and most significantly stated that the report of this independent body would be released for public review and comment without revision by any body of the MMA. To do otherwise would identify the report as a self-serving document stripped of its credibility and potential impact. Secondly, the Board accepted the key role played by physicians in cost determination. Although physicians' fees constitute a relatively small part of the health dollar, physicians are directly or indirectly responsible for a very high percentage of health care expenditures, as they purchase the medical and health care for their patients.

The major thrust of the report clearly addresses the currently operating incentives that shape the performance of the system and the behavior of the people functioning within it. The rational for this approach is addressed in detail in the Commission's Report which is piggybacked with this issue of MINNESOTA MEDICINE. The report clearly focuses on the strategies it considered essential to bring meaningful and lasting changes that address cost containment. The goal is to return cost sensitivity to both the provider and consumer segments. The action considered fundamental by the Commission to actualize these goals address both consumer and provider behavior, cost sharing, and enhancement of a market-oriented, pluralistic delivery system. The Commission, also, adopted 36 other recommendations that expand upon or support these fundamental recommendations and provide the framework and knowledge for continuing alterations in patterns of practice or patterns of behavior once the proper incentives are cultivated.

It has not been the intention of the Commission to offer a laundry list of piecemeal recommendations that do little more than plug a hole here and there and by and large constitute a disciplinary type of motivation that is little more than internal regulation. A strong appeal is made for deregulation to the fullest possible extent, so that true competitive market forces can effectively operate.

It is now incumbent upon the membership of the MMA to address these concepts and recommendations, to assess their impact and lend a maximum of support for these recommendations that they deem appropriate. It is equally important for the Association to comment upon and oppose any recommendation that may seemingly not operate in the public interest. It is already clear that no single group of society can fully endorse the entire report, a fact that supports the independence of the report which is self serving to no segment.

Physicians must look at these recommendations and those to come in the light of their responsibility to protect the quality of medical care, but we also have the intelligence and ability to truly assess quality in terms of medical outcomes and not equate quality with the intensity and cost of the service. The risk of mediocrity in care need not be a product of cost conscious decisions. Expanding bureaucratic rules and regulations are a far greater threat.

The alternative to the effective implementation of those changes which address cost containment is clearly one of ever-increasing government interference until we are irreversibly saddled with a federally financed, federally administered, and federally controlled health care system. For the Association to do nothing in this precious time that remains is to abdicate a basic responsibility, a commitment to best serve the membership and the public interest. The entire membership is urged to study the Commission's report enclosed herewith in detail so that we can leave the annual session in St. Paul in May with a clearly defined consensus and a directive for action by our organization.

Richard J. Frey, M.D.
Chairman, Commission on Health Care Costs

Cover Photo

''Gooseberry Falls''

The cover photo was taken at Gooseberry State Park, by Dr. John E. Lonstein, using a Pentax ES II, Kodachrome II film. Dr. Lonstein was on vacation with his family when the picture was taken.

He is an orthopedic surgeon, Department of Orthopedics, University of Minnesota and practices spine surgery at Gillette Children's Hospital, St. Paul, and Fairview Hospital, Minneapolis.

Annual Meeting

Minnesota Medical Association Annual Meeting
First Annual Racquetball Tourney
Wednesday, May 16
St. Paul, Minnesota
For information contact: Charles MacDonald, M.D., 612-291-8773
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Editor's Notebook

Editor's Report to the House of Delegates

"Long-winded authors I abhor,
and glib, prolific chatterers,
give me the ones who tear and gnaw
their hair and pens to tatters
who find their writing such a chore
they only write what matters."

Piet Hein, *Grooks*,
M.I.T. Press, 1966

This is my fifth Editor's report. I shall be as short-winded as possible and shall write about what matters.

My custom in these reports has been to: (1) submit my budget request for the coming year and to justify that request, (2) tell you what to expect in the journal next year, and (3) give you an inkling of my editorial philosophy. You have responded favorably to this procedure, so I shall not tinker with it.

Budget Request and Justification

This year I am going to ask for $60,000 for the journal, even though the Minnesota Physicians' Roster, which runs at least $7,500 a year, is no longer part of the budget of MINNESOTA MEDICINE. Last year I insisted the Roster be removed from the MINNESOTA MEDICINE budget. In doing so, I may have done a favor for the Association, for a third party provider may pick up the Roster's expense.

But I digress. Back to my budget request of $60,000. This may sound high to you. Consider it in light of these figures:

Year	Budget	% Increase (approx.)	Financial Performance	Pages per issue	Expense per page	% Increase (approx.)
1975	$40,000	0%	$1,163 under budget	76	$42.59	10%
1976	$44,000	10%	932 under budget	74	$48.50	14%
1977	$46,000	5%	8,010 over budget	75	$60.01	24%
1978	$56,000	22%	475 over budget	61	$77.11	29%
1979	$60,000	7%	data not yet known*	70		

(first 3 months not known).

I do not wish to over analyze these numbers. Just cast your eyes to the last two columns. Note that our expense per page is escalating at an astonishing rate. We have tried to offset these expenses by engaging the services of four commissioned local advertising representatives in the last three years. But these representatives have enjoyed only modest success — not enough to make up for increased production expenses. We have also solicited bids from other printers. None have countered with bids lower than our present printer. So I find myself with two choices: (1) asking you for more money; or (2) reducing the size of the journal.

I have reduced the size of the journal as much as I care to. As recently as 1969, the average monthly issue was 165 pages and the cost per page was 1/3 of what it is now. Let me be blunt about further reducing the size. I do not wish to remain as Editor if MINNESOTA MEDICINE has to become a gaunt ghost of its former self, i.e. 50 pages or less. A medical journal serves two constituencies — its readers and its contributors. Not many readers have complained, but I am catching hell from contributors, many of whom have been waiting for more than a year for their accepted articles to be published. The strength of MINNESOTA MEDICINE has always been the enthusiasm and quality of its contributors — from the private sector, from the Mayo Clinic, from the University, and from institutions such as Hennepin and Ramsey County Medical Centers. I do not wish to quench their enthusiasm or diminish their quality by pleading poverty.

What to Expect

I have taken steps to control costs, and I shall continue.

1. In the last two months of 1978, we eliminated book reviews, editorials, and the Editor's Notebook from the journal, and postponed many articles, thereby reducing our final deficit from $9000 to less than $500.

2. We now ask authors to pay for colored photographs, for more than the usual number of X-ray plates or illustrations, and for costly last minute corrections,.

3. We are urging authors to prune manuscripts and references before we accept papers.

4. We have requested that supplementary material, included in or accompanying the journal, be paid for by sponsoring outside organizations or separate departments of the Minnesota Medical Association.

Who Pays for What?

For example:

- An outside organization, the American Cancer Society, Minnesota Division, paid for the supplement on cervical cancer that accompanied the March 1979 issue (P.E. Fehr, M.D., Arthur H. Bearon, M.D. and Konald A. Prem, M.D.: Minnesota Cervical Cancer Mortality Study 1971-1972. MINNESOTA MEDICINE Supplement 1:S3-S16, 1979).
- The Socio-economic Division of the Association paid for the published presentation before the Cost Commission of Walter McClure of InterStudy (''Choices for Medical Care.'' MINNESOTA MEDICINE 61:261-271, 1978) and for the Health Care Costs Commission's Report Supplement (''New Directions for Health Care: Report and Recommendations of the Minnesota Medical Association's Commission on Health Care Costs, a 46-page booklet accompanying the May 1979 issue of MINNESOTA MEDICINE).

You can expect us to continue to insist that such costly supplements be paid for outside the budget of MINNESOTA MEDICINE. Our number of pages per issue may increase slightly, so we can catch up on the publication of those articles which have been already accepted. We also are committed to several special issues which we are obligated to publish. We shall, however, limit the number of interviews with important people on vital issues. These interviews have proved popular among readers but are space-consuming.

Other Thoughts

Asking for more money is never easy, especially in these times when the Minnesota Medical Association is trying to respond to many social, economic, and legislative challenges. But the American system is one of challenge and response, and I believe the Association must continue to respond with time, money, and energy.

But let us maintain a sense of proportion. During my editorship, the budget of the Association has grown to just over one million dollars. Of that, roughly 40 percent goes to the Socio-economic Division, 12 percent to the Department of Communications (the monthly newsletter, public relations executive, and to the media) and five percent to MINNESOTA MEDICINE. I don't think five percent is enough for a publication that: (1) informs and educates its readers on scientific and social matters, (2) serves as an outlet for scientific contributors and medical leaders, and (3) is a tangible, concrete and repetitive reminder of the Association's existence for busy practitioners who may complain about the expense of dues.

A final thought. I am asking you to balance scientific and social matters. The reputation of any medical journal rests on its scientific integrity and legitimacy and how well it carries out its informative and educational functions. At the same time, a general medical journal, of which MINNESOTA MEDICINE is a good example, should further the political and social aims of the organization it represents. I happen to be one who believes the political forces opposing nationalizing health care have the upper hand. As long as the private sector contributes three of every five dollars for health care, as it now does; as long as physicians are free to choose their work and their place of residence; and as long as we command enough human resources to provide excellent health care, we should be willing to spend money to protect our relative position. This position and the prestige of this Journal depend on adequate financing.

Richard L Reece MD

MMA Annual Meeting

What's New in Common Skin Diseases
3 credit hours Category I / Prescribed
Thursday, May 17, 2:00-5:00 pm, Radisson St. Paul

Course designed for physicians in primary medical practice. Emphasis on diagnosis and therapy (especially recent advances) of dermatologic problems that are currently common. Presentations utilizing 35mm slides, lectures, mini-case presentations and group discussions. Ample time allowed for questions and discussions with a panel. Emphasis on discussion of acne, fungal infections, common alopecias, scabies, and what's new in topical treatment.

Sponsor: Minnesota Dermatological Society

Major Problems in Trauma
3 credit hours Category I / Prescribed
Friday, May 18, 8:30 — 11:30 am, Radisson St. Paul

Lectures to update the current management concepts of colon and rectal injuries, the use of the G-suit in trauma, management regimens of blunt thoracic trauma, and urgent orthopedic injuries. Review of mortality and morbidity resulting from the repeal of the Minnesota Mandatory Motorcycle Helmet Law. Organizational concepts for a rural trauma program. Expert advice on difficult problems of abdominal and thoracic trauma and of hand, orthopedic and plastic surgery problems and of trauma care in the emergency room.

Sponsor: Minnesota Chapter, American College of Surgeons

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Precautions: Symptomatic relief should not delay definitive diagnoses or treatment. If irritation develops, Anusol-HC Suppositories and Anusol-HC Cream should be discontinued and appropriate therapy instituted

In the presence of an infection the use of an appropriate antifungal or antibacterial agent should be instituted If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Care should be taken when using the corticosteroid hydrocortisone acetate in children and infants

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Intestinal Fistula from A Toothpick

PETER A JERNIGAN, M.D.* and GERALD T. MULLIN, JR., M.D.†

A 61-year-old man perforated his duodenum and developed an intestinal fistula from a toothpick. We found this to be such an uncommon event that a literature review was undertaken and is presented.

SWALLOWING A TOOTHPICK is not rare, but an intestinal fistula after toothpick ingestion is uncommon. In this paper we present our experience and review the literature.

Case Report

A sixty-year old white male, retired airline pilot, with longstanding hypertension, previous myocardial infarction, depression, and alcoholism, complained of epigastric and right upper quadrant abdominal pain in October, 1976. Examination at that time was negative. He continued to complain of mild epigastric discomfort, and in February, 1977, he was found to have an easily palpable abdominal aortic aneurysm, subsequently proven by angiography.

He underwent surgery for resection of his aneurysm, and at the time of operation, a colonic mass with adherence to the liver was discovered. Partial hepatectomy and partial colectomy were performed which revealed that the mass was inflammatory. A toothpick was found perforating the third part of the duodenum (Figure 1), forming a fistula into the posterior aspect of the hepatic colon. The duodenal perforation was oversewn and the colon was anastomosed side-to-side. The aneurysm was not resected. The patient died shortly thereafter of complications from the surgery. At autopsy, the site of duodenal perforation could be easily reconstructed (Figure 2).

Discussion

While the incidence of toothpick ingestion is unknown, a toothpick is most likely to be swallowed when it is used as an eating utensil, support for a sandwich, or decoration for food or drink.[12,14,15] Perforations of the bowel by a toothpick account for about ten percent of all intestinal perforations by foreign objects.[6] Davidoff and Towne estimate that actual perforation of the intestinal wall occurs in less than one percent of the instances when a foreign body is ingested.[1]

Factors Favoring

Frequently, no history of ingestion of the toothpick is obtained.[6,7,10,16] This has been related to several factors, the most interesting being wearing dentures.[8,11,12,17] Up to 80 percent of accidental foreign body ingestion in adults occurs in individuals wearing dentures,[17] apparently because the palate loses tactile sensitivity when upper dentures are worn.[9,10,15,16] Other factors associated with accidental toothpick and other foreign body ingestion have been related to drunkenness,[3,13] rapid eating,[9] and mental retardation,[8,13] The risk is increased if the toothpick is hidden in meat or a club sandwich.[15] Our patient was a denture wearer and this, plus his alcoholism, likely contributed to his swallowing the toothpick.

Sites of Perforation

Once a foreign body is swallowed, the anatomy of the intestinal tract is such that there are certain areas

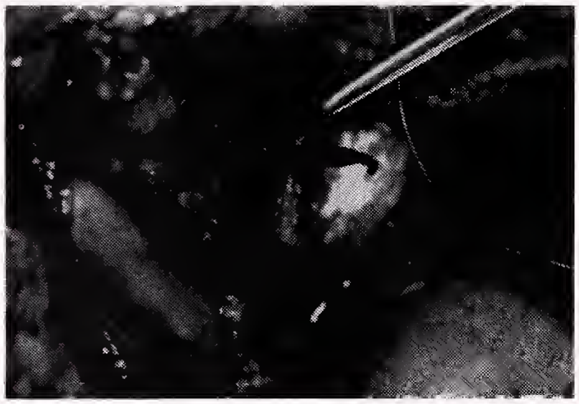

Figure 1

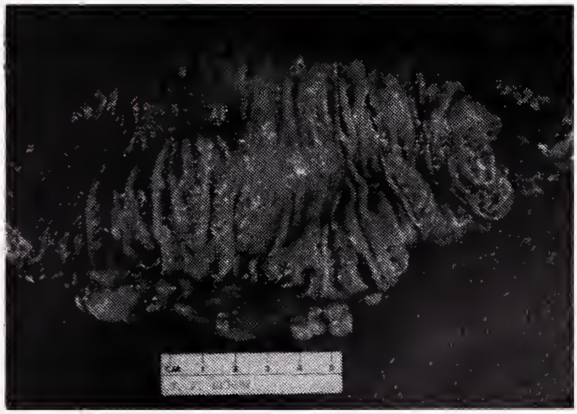

Figure 2

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*Third-year Family Practice Resident, St. Mary's Hospital, Minneapolis.
†Staff physician, St. Mary's Hospital, Minneapolis.
See editorial, page 337.

that seem pre-disposed to perforation. Eitel states that a long, sharp object, such as the toothpick, has a predilection for lodging in the second or third portions of the duodenum, because of the difficulty in making the sharp turn that the duodenum takes.[2] Our case would fall into this category. Several authors report that the toothpick often perforates the intestine around the ileocecal region, for the same anatomical reason that the duodenum is perforated.[5,6,8] Toothpicks are the most common foreign body to perforate the cecum.[16]

Recognition of an intestinal perforation by a foreign body, such as the toothpick, is rarely made preoperatively. The patient may present as an acute abdomen or without symptoms. With our patient, we don't know if his symptoms were related to his duodenal perforation and fistula or to his aneurysm.

Laboratory studies are of little help. X-rays will not reveal an opaque object, such as a toothpick, and may rarely show free air.[10] St. John theorizes that an air leak through a minute perforation by a toothpick is highly unlikely.[11] Upper gastrointestinal series has occasionally been useful in localizing opaque objects.[2]

Other Complications

Many times intestinal perforations from toothpicks have not been recognized until unusual complications have occurred. Such complications include subcutaneous emphysema, mediastinal perforation, pleurisy, venous and arterial perforations, bladder perforation, and liver and perinephric abscesses. We are adding enteric fistula to this list and would hope that physicians might be made more aware of the possible dangerous complications from toothpick ingestion. We recommend warning patients, particularly denture wearers, of the dangers that may result from the use of toothpicks or similar objects.

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Surgical Treatment of Uremic Pericarditis

DAVID S. HODGE, M.D.,* CHRISTINA M. COMTY, M.D.,* and HOVALD K. HELSETH, M.D.*

Uremic pericarditis remains a frequent complication of renal failure. Although usually controlled with intensive dialysis, a percentage will fail to resolve and become surgical candidates. Elective subtotal pericardiectomy is the treatment of choice for stable patients with pericarditis or effusion refractory to medical therapy. In unstable patients, subxyphoid window can be an effective alternative. Both operations can be performed with low morbidity and mortality.

EVEN WITH THE present day use of widespread hemodialysis, pericarditis remains a frequent complication of renal failure.[1,3,7,11] The clinical manifestations of uremic pericarditis vary from an asymptomatic effusion to cardiac tamponade. Management consists of frequent dialyses possibly combined with corticosteroids or Indomethacin. With such medical therapy a percentage fail to resolve their pericarditis and become suitable candidates for surgery. In our experience both subxyphoid pericardial window and subtotal pericardiectomy via anterior thoracotomy have been used successfully. This review of our past ten years' experience would seem to support present reports that formal pericardiectomy is preferred treatment for stable patients with pericarditis or effusion refractory to medical therapy.[4,6,9,10,12,13]

Patients and Methods

Over the 10 year period (1966-1976) 717 patients were initiated on chronic hemodialysis at the Regional Kidney Disease Program in the Hennepin County Medical Center, Minneapolis, Minnesota. Since 1970 all patients were treated with thrice weekly dialyses using initially the standard Kiil dialyzers and more recently Dow-4 and Gambro dialyzers. Dialysis was performed in the parent center in Minneapolis, in multiple satellite units in the five state area or in the patient's home.

Pericarditis was considered in the differential diagnosis in all patients with unexplained fever of 99°F or more; unexplained hypotension during dialysis; rapid weight gain without hypertension; pain in the chest, neck or shoulders; cardiomegaly on routine chest films, or the onset of an arrhythmia. Screening procedures included physical examination, chest Xray, EKG, central venous pressure measurement, heart scan, and echocardiography. The diagnosis of pericarditis was made if a friction rub was heard or the heart scan or echocardiogram was positive in the absence of a friction rub. A patient was considered for surgery if: (1) he developed cardiac tamponade; (2) the pericardial effusion failed to resolve after a period of intensive dialysis combined with anti-inflammatory drugs; (3) the pericardial effusion reaccumulated after withdrawal of anti-inflammatory drugs; (4) blood pressure instability prevented intensive dialysis therapy; (5) cardiomegaly, pain, and fever persisted; or (6) constrictive pericarditis developed. Of the 190 patients, 35 required surgery by one or more of these criteria.

All patients requiring surgery were undergoing regular hemodialysis at the onset of their pericarditis. The duration of dialysis was less than six months in 17 and greater than six months in 18 patients. Pericarditis was present for an average of two weeks prior to surgery.

Results

Pericardiocentesis proved to be uniformly unsuccessful. Seven of eight patients required surgery because of the failure of pericardiocentesis to relieve their symptoms. One patient treated by pericardiocentesis alone continued to have symptoms relieved in part with steroids prior to her death. The use of pericardiocentesis alone as definitive treatment of uremic pericardial effusions has been abandoned in our institution as in others.[4,9,12,13]

Twenty-one patients had their effusions relieved by the formation of a pericardial window. Initially they were created via thoracotomy. However, since 1970 the subxyphoid approach has been utilized in this group. Five patients died within one week of surgery. Seven patients died two months to 2½ years following their operation of causes probably unrelated to their pericarditis. Autopsy examination of these patients revealed extensive adhesive pericarditis in all. Nine are alive, three with functioning transplants and six on chronic hemodialysis. The major complication occurring in five patients was persistent pericarditis with fever, rub or chest pain. Pleural effusions occurred in three other patients.

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Subtotal pericardiectomy was used to relieve pericarditis and effusions in 13 cases. In this group there were no early deaths. Three late deaths at seven, eight, and 12 months have occurred. Complications include two pleural effusions, one pneumonia and one persistent fluid production requiring a pericardial catheter for two weeks. Five patients have undergone transplantation and five remain on chronic hemodialysis. One patient required a total pericardiectomy for constrictive pericarditis.

Discussion

Pericarditis, with or without effusion, frequently complicates the course of the patient with renal failure. Control of the biochemical aberrations with hemodialysis has reduced the incidence but it is still a significant problem for a large number of patients. Generally the majority of cases can be safely and successfully managed with intensive dialysis. The value of anti-inflammatory drugs in conjunction with intensive dialysis is unclear.[3,5,8] Both Prednisone and Indomethacin have been used in our institution with inconclusive results. Intrapericardial instillation of steroids has been used elsewhere.[2] We have no experience with this technique.

When the medical regimen of intensive dialysis with or without drugs fails to relieve the patient of symptoms or signs of pericarditis, surgery becomes indicated. Surgery is also indicated during medical treatment if the patient becomes unstable, making intensive dialysis impossible, or if he develops cardiac tamponade.

In the latter urgent situations, we prefer to use the subxyphoid pericardial window with local anesthesia. Often these patients are unstable and not suitable candidates for general anesthesia. In this select group the subxyphoid approach has proved successful. If pericarditis persists or recurs after subxyphoid window then a more definitive sub-total pericardiectomy should be performed when the patient is stable and without further medical therapy.

Early in this series the subxyphoid window was used in some stable patients with persistent effusions and symptoms of pericarditis. Although successful in relieving the effusions, five patients treated in this manner had persistent pericarditis with fever, pain and friction rubs. Four patients were restarted and maintained on steroids for variable periods of time. It would have seemed more appropriate to recommend these patients for subtotal pericardiectomy rather than to persist with medical treatment, particularly since the long-term outlook for all was favorable.

Elective subtotal pericardiectomy is now our preferred treatment in cases of pericarditis refractory to medical therapy. This approach would seem to agree with the experience reported from other institutions.[4,6,9,10,12,13] The morbidity and mortality from the procedure is low and relief is excellent. No persistence or recurrence of pericarditis has occurred in this group.

Mention should be made of the seven diabetic patients on chronic hemodialysis in this group. Consideration should be given to early pericardiectomy, as medical management is less successful and has a higher morbidity in these patients.

Summary

Pericarditis continues to be a problem in patients on hemodialysis. Subtotal pericardiectomy is a safe and effective method of treating pericarditis and is the procedure of choice in patients unresponsive to medical therapy. In the acute situation, and the older, unstable patient, subxyphoid window can be an effective form of therapy.

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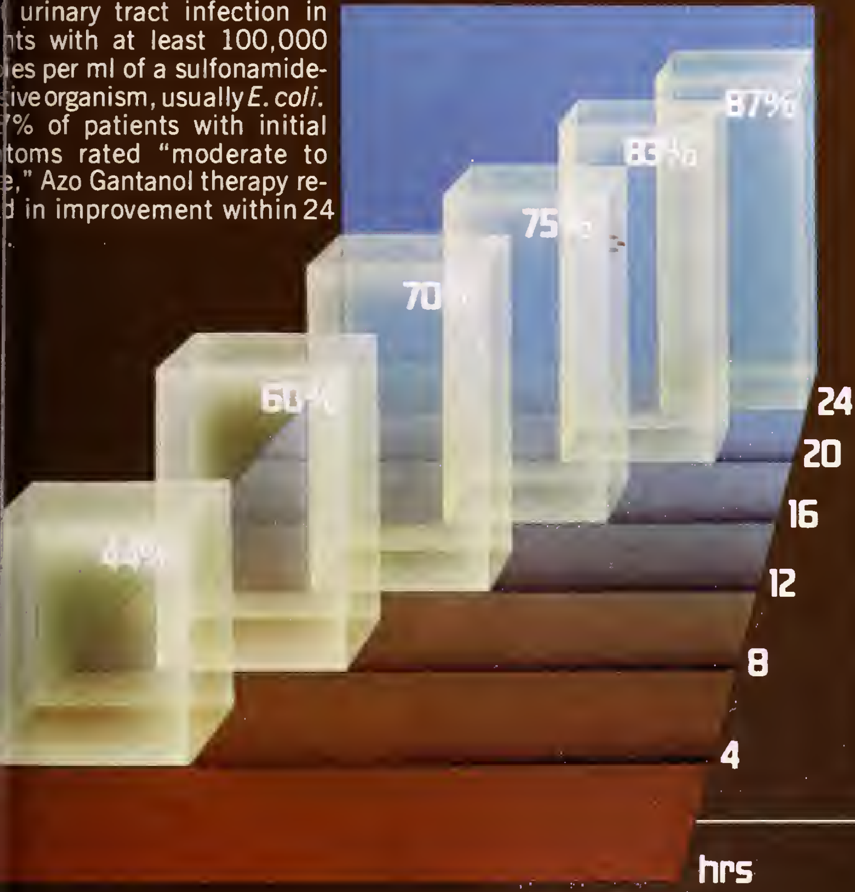

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Indications: In adults, urinary tract infections complicated by pain (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period; because Azo Gantanol contains phenazopyridine hydrochloride it is contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with G.I. disturbances.

Warnings: Safety during pregnancy not established. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, Stevens-Johnson syndrome, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *G.I. reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Azo Gantanol is intended for the acute, painful phase of urinary tract infections. *Usual adult dosage:* 2 Gm (4 tabs) initially, then 1 Gm (2 tabs) B.I.D. for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment with Gantanol (sulfamethoxazole) may be considered.

NOTE: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine.

Supplied: Tablets, red, film-coated, each containing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 500.

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- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age. Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and int mittent abdominal pain have been reported.

Vascular: There have been rare instances of a gener ized hypersensitivity vasculitis or necrotizing angii which have led to irreversible hepatotoxicity and dea

Hematopoietic: Agranulocytosis, anemia, aplast anemia, bone marrow depression, leukopenia, panc topenia and thrombocytopenia have been report in patients, most of whom received concomitant dru with potential for causing these reactions. Zyloprin (allopurinol) has been neither implicated nor exclud as a cause of these reactions.

Neurologic: There have been a few reports of peripher neuritis occurring while patients were taking Zylopri Drowsiness has also been reported in a few patient

Ophthalmic: There have been a few reports of catarac found in patients receiving Zyloprim. It is not know if the cataracts predated the Zyloprim therapy. "Toxi cataracts were reported in one patient who al received an anti-inflammatory agent; again, the ti of onset is unknown In a group of patients follow by Gutman and Yü for up to five years on Zylopri therapy, no evidence of ophthalmologic effect attrib able to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idi syncrasy have been reported in a few patients. Th was characterized by fever, chills, leukopenia or leuk cytosis, eosinophilia, arthralgias, skin rash, pruritu nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poiso ing, by Zyloprim has not been reported.

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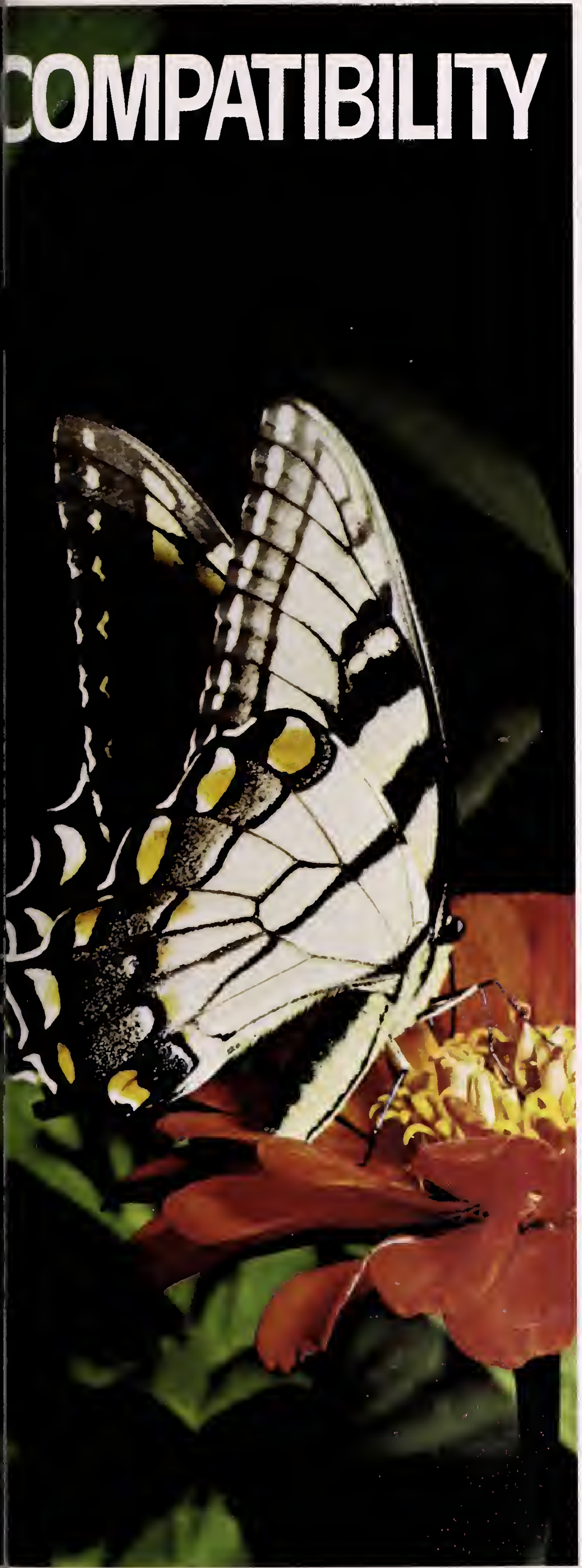

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Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg. Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily. Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted.

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed.

Supplied: Tablets, 10 mg., bottles of 100, 1000, 5000 and Unit Dose; Tablets, 20 mg., bottles of 100, 500, 1000, 5000 and Unit Dose; Injection, 10 mg. per 2 ml. ampul, box of six 2 ml. ampuls.

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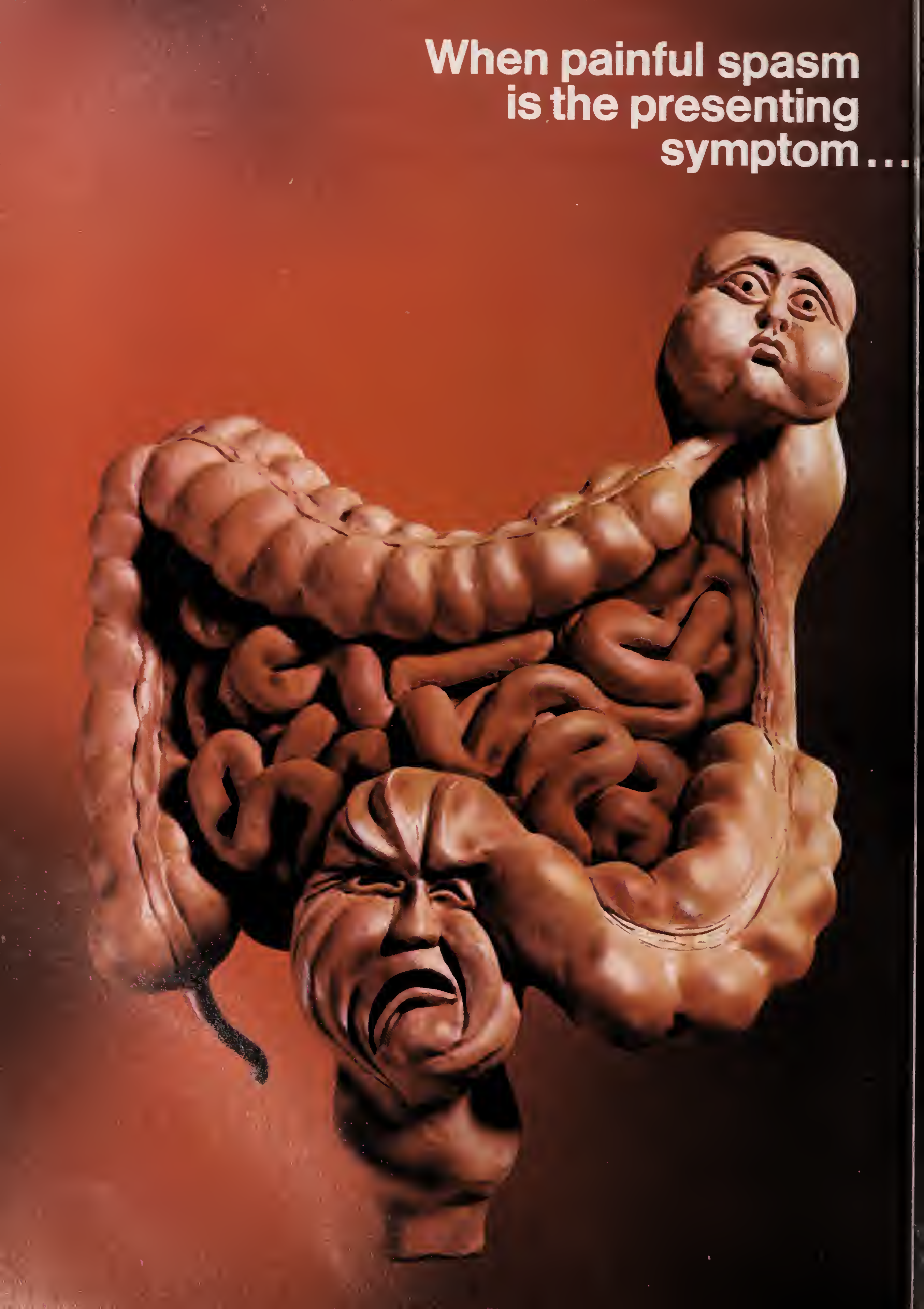
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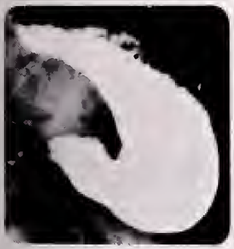
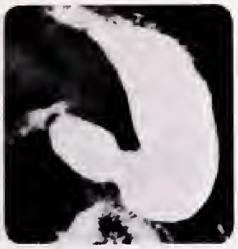
. . . Bentyl produced definite relaxation in 8 of 10 patients. The sodium chloride produced relaxation in only 3 of 10. No side effects occurred in either group of patients.



Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Brief Summary

INDICATIONS
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache, nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation, bloated feeling, severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs

Usual Dosage Bentyl 10 mg capsule and syrup: *Adults* 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children* 1 capsule or teaspoonful syrup three or four times daily. *Infants:* ½ teaspoonful syrup three or four times daily (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults:* 1 tablet three or four times daily. Bentyl Injection: *Adults* 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE. The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine™ (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

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Cerebral Tuberculoma

JOHN R. MAWK, M.D.,* MAHMOUD G. NAGUIB, M.D.,* JESSE C. YAP, M.D.*
and SHELLEY N. CHOU, M.D., Ph.D.*

Tuberculosis involving the central nervous system is an uncommon disease in Minnesota, only five cases having been reported in a 42 month period. In areas of the world where tuberculosis is endemic, tuberculoma is very common, but in this country it is quite unusual and is more likely to be confused with a brain abscess or brain tumor preoperatively. The authors report a case of cerebral tuberculoma in which the diagnosis eluded pathological or microbiological confirmation during life in spite of numerous attempts at biopsy. Appropriate drug therapy did not alter the course of the disease. Although vigorous medical and surgical therapy are indicated in all cases, this disease may pursue a relentless course.

SINCE THE INTRODUCTION of antitubercular drugs some thirty years ago, tuberculosis has dwindled in significance as a public health problem. Between January 1975 and July 1978, 723 new cases of tuberculosis were registered in the Minnesota Department of Health. Involvement of the central nervous system was reported in five cases during this period; thus, the proportion of all new cases of tuberculosis in this state which manifest central nervous system involvement is less than 1%.

As any disease grows less common, its recognition becomes more difficult. In the following case, the patient was correctly treated based on the presumptive diagnosis of cerebral tuberculoma. In spite of vigorous medical and surgical therapy, he expired. Problems associated with the confirmation of the diagnosis are discussed, as well as the typical features of cerebral tuberculoma.

Case Report

A twenty-six-year-old black male fell while running. Although he had not lost consciousness, he complained of headache and right-sided weakness when seen at a local hospital. Examination at the time of admission showed that the patient was awake and alert, afebrile and had a mild right hemiparesis. Past history included a central cervical cord syndrome from which the patient had recovered, as well as post-traumatic constrictive pericarditis, which had been treated with pericardial fenestration. There was a strong family history of tuberculosis; the patient's tuberculin skin test had been positive in the past, but he had never been on any anti-tubercular drugs. Admission laboratory tests and skull Xrays were normal.

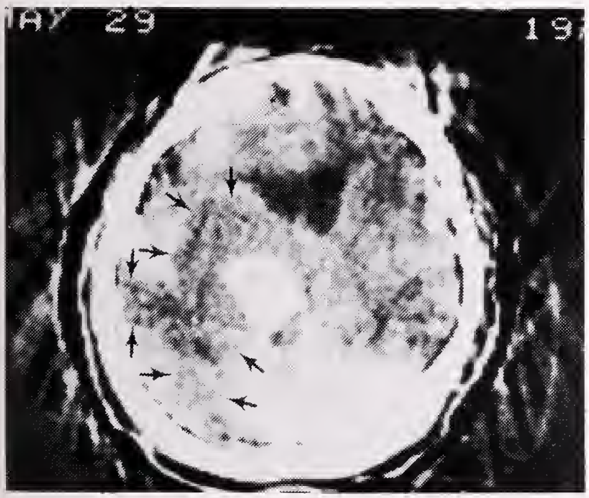

Figure 1 — Computerized tomographic scan demonstrating high-density lesion with lucent center in the region of the left pulvinar nucleus. Arrows delineate large zone of surround lucency which probably represents cerebral edema. Note to the left-to-right shift of midline structures.

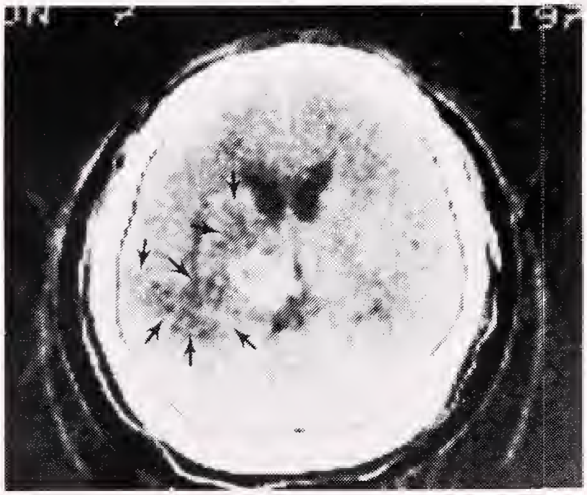

Figure 2 — Repeat CT scan showing resolution of left-to-right shift, slight decrease in size of the lesion and significant decrease in the zone of surround edema (arrows) following administration of steroids.

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*Department of Neurosurgery, The University of Minnesota Health Science Center, Minneapolis, Minnesota.

Over the next two days his level of consciousness deteriorated. An electroencephalogram demonstrated bifrontal slowing. A temperature spike to 39.3 C occurred on the third day, accompanied by the sudden development of meningeal signs. A lumbar puncture yielded fluid under increased pressure; the glucose was 30 mg%, Cl 104 mEq/L, protein 510 mg%, red cells 170/cu mm and white cells 540/cu mm with 90% polymorphonuclear forms. Penicillin and chloramphenicol were instituted. Cultures subsequently grew microaerophilic Streptococcus.

Worsening of the hemiparesis prompted a computerized tomographic (CT) scan (Figure 1). This demonstrated a well-circumscribed mass in the posterior left thalamus with a central lucent zone. There was extensive surrounding edema with a left-to-right shift. This mass was interpreted as an abscess, but tumor was listed as an alternative possibility.

The patient was placed on steroids. He improved gradually, but never regained his admission neurologic status. The peripheral white count hovered around 20,000. Meningeal signs resolved, however. He was placed on INH, rifampin and pyridoxine, based on his past positive skin test. A repeat CT scan showed resolution of the left-to-right shift due to a slight decrease in the size of the mass itself as well as a substantial decrease in the surrounding zone of edema (Figure 2). The patient was then transferred to the University of Minnesota Hospitals for a proposed needle biopsy and/or drainage procedure.

A left parietal burr hole was made and biopsy was attempted at two separate sittings. During the first attempt the needle encountered a firm mass in the region of the left pulvinar nucleus. No cyst was entered. Tissue fragments showed gliosis of low grade. Ventricular CSF removed at that time showed a sugar of 78 mg%, protein 106 mg%, 3500 red cells/cu mm and 328 white cells/cu mm with 95% mononuclear forms. The second biopsy was carried out during fractional pneumoencephalography in order to better delineate the thalamic mass. Once more, the tissue showed only gliosis. Cerebrospinal fluid was sent for culture on both occasions.

A formal stereotaxic biopsy was then performed through a left frontal burr hole. A cyst encountered in the posterior-superior portion of the left thalamus contained about 3 cc of turbid, bloody fluid filled with hosts of cells and cellular debris. The small amount of tissue obtained was fluoresceinpositive, suggesting the possibility of a neoplasm.

In spite of ongoing anti-tubercular therapy, the patient died during the second month of his illness. Shortly after his death the cultures obtained during the first and second biopsy attempts grew Mycobacterium tuberculosis.

Autopsy disclosed a tuberculoma within the posterior portion of the left thalamus (Figure 3). The lesion was solid but was ringed with small hemorrhages which were felt to be related to the biopsy attempts. The small cavity entered at the time of stereotaxic biopsy was likely the most superior of these hemorrhagic regions.

Microscopic examination disclosed findings typical of a tuberculoma (Figure 4). The lesion was surrounded by a poorly organized collagenous •pseudocapsule. The central portion of the lesion consisted of caseous necrosis. An intermediate zone of inflammatory mononuclear infiltration was punctuated by occasional clumps of epithelioid cells and rare giant cells.

Discussion

Chronic meningitis is the most common form of CNS tuberculosis. Tuberculoma is second in order of occurrence. By definition, a tuberculoma is a mass resulting from enlargement or coalescence of caseous tubercles. The older literature stressed the frequent contamination of the cerebrospinal fluid with organisms shed from a tuberculoma. This is very probably what occurred in our own case; we believe the Streptococcus found on the initial culture was a skin contaminant. The high protein is characteristic of tuberculous meningitis. The polymorphonuclear pleocytosis, while more characteristic of a bacterial process, by no means detracts from the diagnosis of tuberculous meningitis.

Drug treatment must be instituted once the diagnosis of tuberculoma has been entertained. Although no data exist on the penetrance of antitubercular drugs into cerebral tuberculomas, medical therapy is the keystone of the therapeutic assault of this disease. Multiple intracranial tuberculomas have been successfully managed by intensive drug therapy coupled with

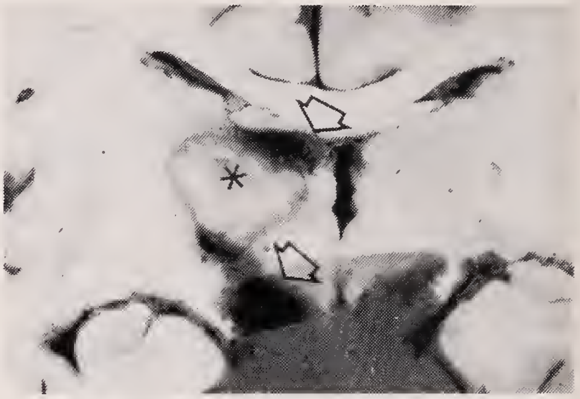

Figure 3 — Postmortem gross specimen demonstrating large lesion in the left thalamus. Central zone of necrosis marked with an asterisk. Arrows point to hemorrhages surrounding the lesion, which are likely related to the biopsy attempts.

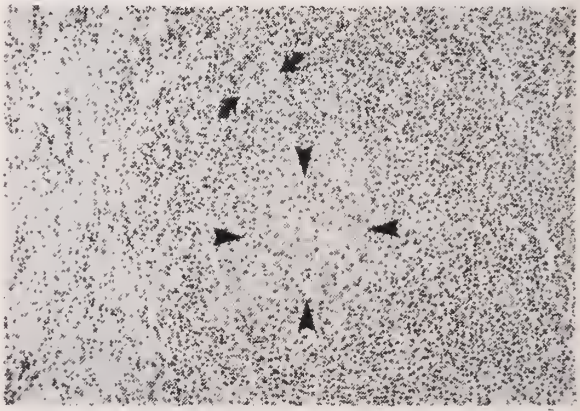

Figure 4 — Microscopic examination of specimen revealing three distinct zones within the tuberculoma. A fibrous pseudocapsule is seen on the left side of this photomicrograph. Two giant cells of the Langhan's type (curved arrows) lie within the stroma composed principally of lymphocytes. A cluster of epithelioid cells (arrowheads) is also seen.

surgical resection of the larger lesions. Most cerebral tuberculomas are in surgically accessible locations, such as the cerebral or cerebellar hemispheres. These should be extirpated at the earliest possible time. Our patient had a tuberculoma deep within the thalamus. Surgical excision, although technically feasible, would very probably be attended by the development of severe, persistent neurologic deficit. Recently, Dierssen and his co-workers in Spain reported the extremely heroic, successful removal of a tuberculoma from within the substance of the mesencephalon[2].

It was difficult to prove the suspected diagnosis in our patient. Other authors have pointed out the various forms in which cerebral tuberculoma may masquerade. These include bacterial brain abscess[9] and cystic glioma[6]. The CT scan appearance is nonspecific. Price and Danziger noted high-dense, low-dense and isodense tuberculomas in their series[5]. In our own case, the brain tissue surrounding the tuberculoma fluoresced following the intravenous administration of fluorescein dye. This is a nonspecific finding due to disturbance of the blood-brain barrier.

There is some evidence that tuberculoma of the brain might be slowly rising in occurrence rate. Several small series[1,4,5] call attention to the problem of recognizing this unexpected pathology.

Conclusion

Tuberculous involvement of the central nervous system, although rare in Minnesota, must always be considered in the differential diganosis of mass lesions of the nervoys system. Appropriate drug therapy must be instituted early, before microbiological confirmation of the disease. Surgical extirpation of most cerebral tuberculomas should be performed early in the course of the disease. Involvement of the deep structures of the brain may make definitive diagnosis and surgical treatment difficult.

Acknowledgment

The authors wish to thank Drs. Richard Siebert, David Danoff and Sidney Shapiro for providing clinical and laboratory information pertinent to this case. We also extend our gratitude to Ms. Allain Hankey, M.S., of the Division of Communicable Diseases, Minnesota Department of Health, for compiling the disease statistics for us.

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Editorials

Malignancy of the Ovary

IN THIS ISSUE an article by Campaigne* summarizes the combined experience of three Duluth hospitals in the treatment of ovarian cancer. The author is to be commended for this study. A report such as this allows a comparison of results of treatment of ovarian cancer in the community with those of cancer treatment centers where care is provided by highly skilled gynecologic oncologists. More studies such as this should be undertaken to evaluate the results of community based cancer treatment.

It is appropriate that this study was addressed to ovarian cancer. Although the third most common malignant disease of the lower female generative tract, cancer of the ovary has vaulted into the number one position as a killer of women, leading all other gynecologic malignant disease. The prevalence of ovarian cancer has not increased. In terms of early diagnosis and treatment progress in ovarian cancer does not compare with the more prevalent cancers of the uterine cervix and corpus.

This study again points out facts about ovarian cancer that need emphasis. The disease is not usually discovered in its early stages. Although 31.5% of the women in this study had disease limited to the ovaries, and therefore Stage I, this is usually not the case. Studies have shown that Stages I and II are frequently underdiagnosed and can be affirmed only if a meticulous surgical exploration of the abdomen, liver, pelvis, diaphragm and retroperitoneal lymph nodes is made. Although the disease is often said to be limited to one or both ovaries (Stage I) or the pelvis (Stage II) the exploration was not sufficiently thorough and tumor spread was overlooked. Two studies have shown that re-exploration or laparoscopy within one month of the initial laparotomy found subdiaphragmatic metastases in 31-44% of women with Stage I-II disease.[1,2] Other reports have shown that para-aortic lymph node metastases are not uncommon in gynecologic malignancies presumed to be confined to the pelvis.[3,5]

Too frequently laparotomy is performed through a short infraumbilical or transverse lower abdominal incision of such length that a thorough exploration of the upper abdomen is impossible. These incisions are contraindicated when ovarian malignancy is seriously included in the differential diagnosis. Inadequate exploration may explain why the five year survival rate of 50% for Stage I and 19% for Stage II in this series, is significantly lower than the 65% and 30% or higher survival rates reported.[4]

In the Duluth series unilateral oophorectomy was performed in 10.1% of the cases of Stage I disease because of nulliparity. It should be emphasized that unilateral oophorectomy regardless of age or parity is inappropriate therapy except when the histologic diagnosis is dysgerminoma, granulosa cell tumor, or mucinous cystadenocarcinoma[6] and preservation of reproductive function is a primary concern. Other epithelial ovarian malignancies carry a much higher bilateral risk and conservative therapy should not be undertaken regardless of age or desire for reproduction.

The cornerstone in the management of ovarian cancer is surgery — even when the disease is advanced. Subsequent chemotherapy or radiotherapy is most effective when the advanced disease has been effectively "debulked". Debulking should be as extensive as is consistent with the experience of the surgeon and the patient's overall medical condition. It should include pelvic and para-aortic lymph node sampling. The results of post-surgical treatment for Stages II and III are consistently and significantly better when all gross disease has been removed ("optimal stage") than when incompletely removed ("suboptimal stage").[4] Sixty percent of the Stage III cases in this survey only had a biopsy taken — this appears to reflect a lack of aggressive surgical debulking.

Chemotherapy, as indicated in the survey, is gradually replacing radiation therapy as the preferred adjunctive treatment after surgery. Chemotherapy is systemic therapy whereas radiation is local therapy which cannot, considering the pattern of spread of ovarian carcinoma, be administered to the whole abdomen and pelvis in cancerocidal dosage.

Radioactive materials such as chromic phosphate and colloidal gold used in this study to treat ascites have been shown to be useful only in Stage I disease because the beta radiation emitted from the materials has limited tissue penetration and is effective only against tumor particles that are millimeters in size or smaller. As used in this study when ascites is present the disease is usually wide-spread and will not be

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*See page 360.

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significantly affected by these materials.

The specialty of obstetrics and gynecology has long recognized that the management of not only ovarian cancer, but all gynecologic cancer frequently demands more than one modality of treatment regardless of the extent of the disease. It has therefore established additional training requirements for gynecologists interested in gynecologic oncology and certification in that subspecialty. With training in abdominal and radical pelvic surgery, gynecologic pathology, chemotherapy and the principles of radiation therapy, the gynecologic oncologist provides continuity of care and the capability of managing most of the problems of therapy and the complications of the disease.

Konald Prem, M.D.*
Minneapolis, Minnesota

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*Head, Department of Obstetrics and Gynecology, University of Minnesota, Minneapolis.

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Intestinal Fistula from A Toothpick

THE ARTICLE on "Intestinal Fistula from a Toothpick" as described by Jernigan and Mullin,* describes a fascinating complication from a foreign body ingestion. Unfortunately for the patient, it would have been just as well if it had not been discovered for he died of postoperative complications. The fistula had not been diagnosed preoperatively and this reader wonders if the resection was carried out on an unprepared bowel.

The right upper quadrant pain could have alerted the authors toward the possibility of a lesion other than the aneurysm being present and GI studies might have demonstrated the fistula.

In a case such as this, more than one lesson can be learned and the readers should be grateful to Drs. Jernigan and Mullin for publishing the interesting case history.

Harrison H. Farley, M.D.
Minneapolis, Minnesota

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*See page 321.

Phenylbutazone-Induced Hepatitis

DR. MAYER'S* FINE review and case presentation highlight the role of drugs and related hepatotoxicity. In the instance described, the patient developed a clinical and biochemical picture consistent with a drug reaction and this was subsequently confirmed by closed needle biopsy of the liver.

The clinical findings, of course, may mimic acute biliary tract disease and, accordingly, a careful drug history must always be sought in the presence of abnormal liver function tests.

The case serves notice to all clinicians to be aware of the potential risks and possible harmful hepatotoxic effects of many commonly used pharmacologic agents. These might include alpha methyldopa, isoniazid, salicylates, antibiotics (e.g., erythromycin estolate), and anticonvulsants (e.g., dilantin).

Joseph M. Tombers, M.D.
Minneapolis, Minnesota

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*See page 349.

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MINNESOTA MEDICINE's Best of the Year

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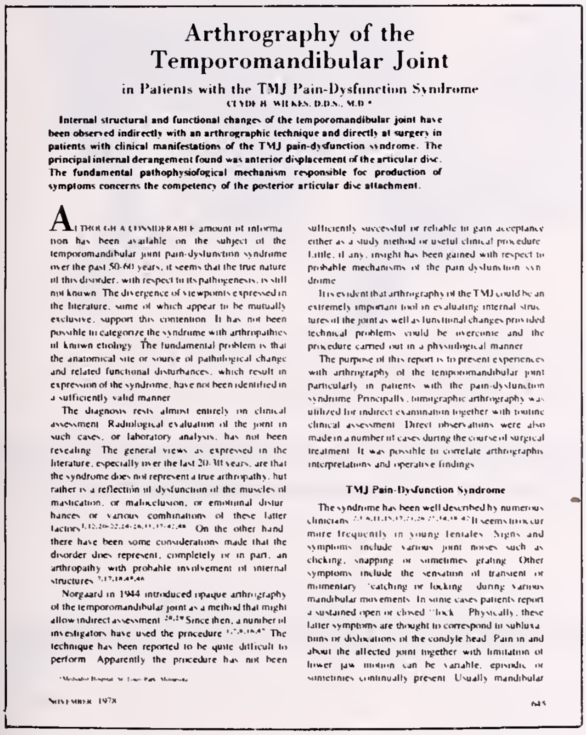
Best Articles



Arthrography of the Temporomandibular Joint

in Patients with the TMJ Pain-Dysfunction Syndrome

CLYDE H. WILKES, D.D.S., M.D.*

Internal structural and functional changes of the temporomandibular joint have been observed indirectly with an arthrographic technique and directly at surgery in patients with clinical manifestations of the TMJ pain-dysfunction syndrome. The principal internal derangement found was anterior displacement of the articular disc. The fundamental pathophysiofogical mechanism responsible foc production of symptoms concerns the competency of the posterior articular disc attachment.

ALTHOUGH A CONSIDERABLE amount of information has been available on the subject of the temporomandibular joint pain-dysfunction syndrome over the past 50-60 years, it seems that the true nature of this disorder, with respect to its pathogenesis, is still not known. The divergence of viewpoints expressed in the literature, some of which appear to be mutually exclusive, support this contention. It has not been possible to categorize the syndrome with arthropathies of known etiology. The fundamental problem is that the anatomical site or source of pathological change and related functional disturbances, which result in expression of the syndrome, have not been identified in a sufficiently valid manner.

The diagnosis rests almost entirely on clinical assessment. Radiological evaluation of the joint in such cases, or laboratory analysis, has not been revealing. The general views as expressed in the literature, especially over the last 20-30 years, are that the syndrome does not represent a true arthropathy, but rather is a reflection of dysfunction of the muscles of mastication, or malocclusion, or emotional disturbances or various combinations of these latter factors.[1,12,20-22,24-26,33,37-42,48] On the other hand, there have been some considerations made that the disorder does represent, completely or in part, an arthropathy with probable involvement of internal structures.[7,17,18,45,46]

Norgaard in 1944 introduced opaque arthrography of the temporomandibular joint as a method that might allow indirect assessment.[28,29] Since then, a number of investigators have used the procedure.[3,7,8,16,47] The technique has been reported to be quite difficult to perform. Apparently the procedure has not been sufficiently successful or reliable to gain acceptance either as a study method or useful clinical procedure. Little, if any, insight has been gained with respect to probable mechanisms of the pain dysfunction syndrome.

It is evident that arthrography of the TMJ could be an extremely important tool in evaluating internal structures of the joint as well as functional changes provided technical problems could be overcome and the procedure carried out in a physiological manner.

The purpose of this report is to present experiences with arthrography of the temporomandibular joint particularly in patients with the pain-dysfunction syndrome. Principally, tomographic arthrography was utilized for indirect examination together with routine clinical assessment. Direct observations were also made in a number of cases during the course of surgical treatment. It was possible to correlate arthrographic interpretations and operative findings.

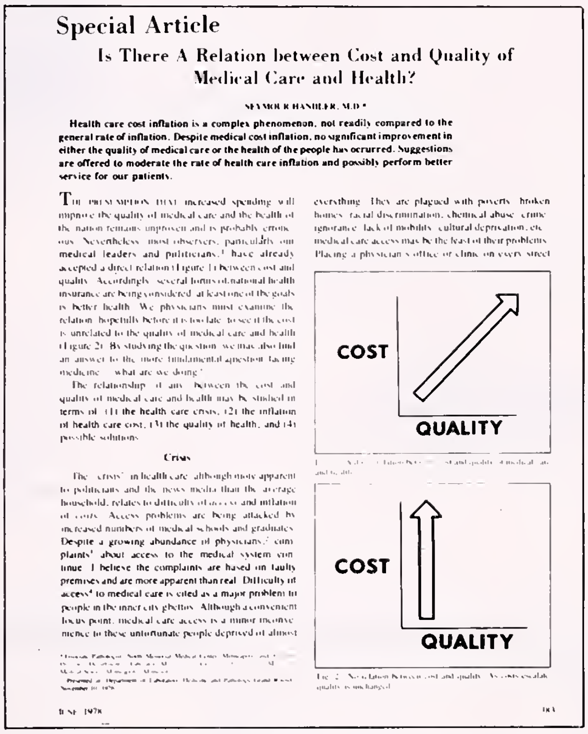
TMJ Pain-Dysfunction Syndrome

The syndrome has been well described by numerous clinicians.[2,5,6,11,15,17,21,26,27,34,35,42] It seems to occur more frequently in young females. Signs and symptoms include various joint noises such as clicking, snapping or sometimes grating. Other symptoms include the sensation of transient or momentary "catching or locking" during various mandibular movements. In some cases patients report a sustained open or closed "lock." Physically, these latter symptoms are thought to correspond to subluxations or dislocations of the condyle head. Pain in and about the affected joint together with limitation of lower jaw motion can be variable, episodic or sometimes continually present. Usually mandibular

*Methodist Hospital, St. Louis Park, Minnesota

NOVEMBER 1978 645

"Arthrography of the Temporomandibular Joint in Patients with the TMJ Pain-Dysfunction Syndrome" by Clyde H. Wilkes, D.D.S., M.D., oral surgeon practicing in Minneapolis. Published in November, 1978, issue of MINNESOTA MEDICINE, page 645.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Special Article

Is There A Relation between Cost and Quality of Medical Care and Health?

SEYMOUR HANDLER, M.D.*

Health care cost inflation is a complex phenomenon, not readily compared to the general rate of inflation. Despite medical cost inflation, no significant improvement in either the quality of medical care or the health of the people has ocrurred. Suggestions are offered to moderate the rate of health care inflation and possibly perform better service for our patients.

THE PRESUMPTION THAT increased spending will improve the quality of medical care and the health of the nation remains unproven and is probably erroneous. Nevertheless, most observers, particularly our medical leaders and politicians,[1] have already accepted a direct relation (Figure 1) between cost and quality. Accordingly, several forms of national health insurance are being considered, at least one of the goals is better health. We physicians must examine the relation, hopefully before it is too late, to see if the cost is unrelated to the quality of medical care and health (Figure 2). By studying the question we may also find an answer to the more fundamental question facing medicine — what are we doing?

The relationship, if any, between the cost and quality of medical care and health may be studied in terms of (1) the health care crisis, (2) the inflation of health care cost, (3) the quality of health, and (4) possible solutions.

Crisis

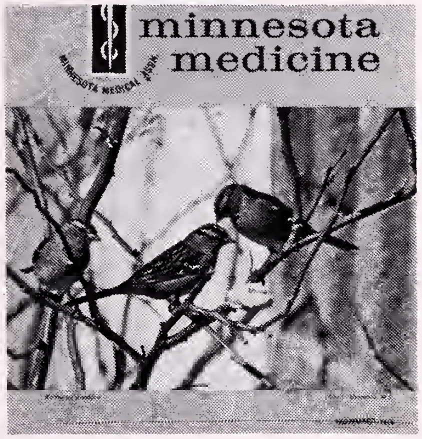
The "crisis" in health care, although more apparent to politicians and the news media than the average household, relates to difficulty of access and inflation of costs. Access problems are being attacked by increased numbers of medical schools and graduates. Despite a growing abundance of physicians,[2] complaints[3] about access to the medical system continue. I believe the complaints are based on faulty premises and are more apparent than real. Difficulty of access[4] to medical care is cited as a major problem to people in the inner city ghettos. Although a convenient focus point, medical care access is a minor inconvenience to these unfortunate people deprived of almost everything. They are plagued with poverty, broken homes, racial discrimination, chemical abuse, crime, ignorance, lack of mobility, cultural deprivation, etc.; medical care access may be the least of their problems. Placing a physician's office or clinic on every street

Fig. 2. No relation between cost and quality. As costs escalate, quality is unchanged.

JUNE 1978 383

"Is There A Relation between Cost and Quality of Medical Care and Health?" by Seymour Handler, M.D., pathologist, North Memorial Medical Center, Minneapolis, and Assistant Professor, Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis. Published in the June, 1978, issue of MINNESOTA MEDICINE, page 383.

Best Cover



"Waiting for Breakfast", November 1978, issue of MINNESOTA MEDICINE by Earl C. Henrikson, M.D., Minneapolis surgeon.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence:* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.
PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.
ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.
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References: 1. Citations available on request—Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M.: A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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Case Report

Phenylbutazone-Induced Hepatitis

THOMAS R. MAYER, M.D.*

A case of hepatitis induced by phenylbutazone is reported. This commonly used medication is noted for gastrointestinal and hematopoietic complications, but hepatic complications, although relatively common, are rarely mentioned. Other case reports are reviewed, and the etiology, pathology, diagnosis, and treatment are discussed.

A 56-YEAR-OLD WHITE woman presented with a three-week history of low back pain radiating into the left buttock and leg. Examination revealed pain in the sciatic notch and weakness of great toe dorsiflexion. She was placed on bedrest and given phenylbutazone (Butazolidin,® Geigy,)100 mg, qid. One week later the patient was pain-free but had weakness on plantar flexion. A subsequent check showed improvement, and the patient returned to her normal activities and stopped the phenylbutazone after a total of three weeks.

One week later, the patient was hospitalized after developing left foot drop. She had run a low-grade fever for the previous four days, supposedly from a mild upper respiratory infection, and on admission had an oral temperature of 100.5 °F. She was put on bedrest with 20 lb of pelvic traction and once again given phenylbutazone (Azolid ®, USV) 100 mg orally, qid.

The following evening her temperature was 103 °F, dropping to 102 °F. the next evening. Chest Xray was normal, and white cell count was 8,500 with 72% neutrophils, 1% band forms, 15% lymphocytes, 9% monocytes, and 3% eosinophils. Two urinalyses were normal. Three blood cultures, two urine cultures, and a sputum culture were negative. The erythrocyte sedimentation rate was 97. SGPT was 70 (normal 0 to 50), with a repeat value of 87, although bilirubin, SGOT, and alkaline phosphatase remained normal. Lumbosacral spine Xrays revealed osteoarthritic changes at L5-S1, and thoracic and lumbar myelography showed an extradural defect at L4-5 on the left, consistent with a herniated disc. Cerebrospinal fluid contained 28 mg. protein, 68 mg glucose, and two monocytes, with a negative smear for malignant cells and a sterile culture.

On the third hospital day, phenylbutazone was discontinued and subsequent temperatures never exceeded 100.8 °F. and were normal within four days. Repeat sedimentation rate was 113. Serum protein electrophoresis revealed mild nonspecific changes and hepatitis-B antigen was negative. Electromyography of the left leg confirmed an L4-5 lesion. Bone scan was normal. Liver scan revealed a normal uptake but mild to moderate hepatomegaly and very mild splenomegaly. Ultrasonic examination of the abdomen and oral cholecystogram were both normal. Percutaneous liver biopsy revealed an eosinophilic granulocytic triaditis consistent with a drug-induced focal hepatitis. On the ninth hospital day, the SGPT was 161, alkaline phosphatase 135 (normal 30 to 115), and the sedimentation rate was 99. Seventeen days later the SGPT was 42, alkaline phosphatase 118, and sedimentation rate 34, and the patient underwent a lumbar laminectomy and L4-5 disc excision with subsequent improvement and no further hepatic problems.

Discussion

The incidence of liver damage from therapeutic drugs is greater than generally recognized, and a better understanding of pharmacokinetics has revealed numerous pathways to increased intrahepatic concentration of drugs and their metabolites, which can lead to liver damage.[1] Although chemical agents damage the liver by either toxic or hypersensitivity mechanisms, most therapeutic drugs cause damage by the hypersensitivity process.[2]

This hypersensitivity process causes a drug-induced hepatitis that can be distinguished from a toxic hepatitis by the following characteristics:[3] (1) it is not reproducible in animals; (2) it affects only a small fraction of exposed individuals (one in 50 to one in 10,000); (3) occurrence and severity are not dose related; (4) the illness has a variable latent period (usually two to five weeks, but a range of from one week to several months); (5) the histologic pattern is variable (cholestatic, hepatic, or mixed); (6) the disorder often is accompanied by extrahepatic manifestations of hypersensitivity (fever, rash, arthralgia, eosinophilia, etc.); (7) illness promptly recurs with a second exposure; and (8) individuals with atopic allergies or antecedant reactions to other drugs often are predisposed. Lymphocyte stimulation and macrophage migration studies indicate that a cell-mediated or delayed hypersensitivity reaction rather than humeral sensitization, accounts for the observed lesions.[3]

Although phenylbutazone is associated with a high incidence of generalized hypersensitivity reactions, hepatitis is a relatively uncommon complication.[4] Forty percent of patients on phenylbutazone will develop untoward side effects that will be severe enough in 15% to warrant discontinuing the medication.[5] Common complications are nausea, edema, dermatitis, abdominal distress, dizziness, and stomatitis, and the more serious complications include peptic ulcer, purpura, agranulocytosis, exfoliative dermatitis, psychosis, and hypertension.[2] However, the incidence of liver damage from phenylbutazone is just under 1%.[2] Anicteric hepatitis, as in this case, has been rarely reported.[3]

---

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See editorial page 337.

Fatalities from hepatitis were more common immediately after the introduction of phenylbutazone in 1952, when higher doses were used and the toxic potential had not been recognized.[6] Among 16 cases of jaundice secondary to phenylbutazone reported between 1954 and 1966, eight patients died. In contrast, of the 25 such cases reported between 1961 and 1972, only three deaths occurred.[6] The sex ratio is 3.5 females to each male, and although all decades over 30 are represented, 75% of patients are more than 50 years old.[6]

The histologic patterns of liver damage that have been recognized with and attributed to phenylbutazone range from the more common pure cholestatic form manifested predominantly by bile stasis and elevated alkaline phosphatase to the pure hepatocellular form with hepatic cell necrosis and serum transaminase elevations, although the predominant pattern is a mixture of these.[1,3,6]

Evidence for establishing the diagnosis of drug-induced hepatitis should include hypersensitivity symptoms, such as fever, rash, eosinophilia, or leukopenia.[2] Onset of symptoms is usually abrupt with fever, chills, rash, arthralgias, often anorexia and nausea or, less frequently, vomiting and abdominal pain. Hepatomegaly may occur, but splenomegaly is rare. Jaundice, dark urine, pruritus, and acholic stools may develop gradually. Exclusion of viral hepatitis often is difficult. Challenge tests are accurate means of establishing drug-induced hepatotoxicity, provided the initial clinical and laboratory abnormalities are completely reversed and a serious reaction is not anticipated.[1] The best available diagnostic tool for this type of injury is liver biopsy, which in addition can document the pattern of injury and its severity.[1]

Treatment for drug-induced hepatitis, besides withdrawal of the sensitizing agent, includes bedrest, B-complex vitamin supplements, and a high protein and carbohydrate diet with fat as tolerated.[2] Steroids do not have any clear-cut benefits, except for pruritus from cholestatic hepatitis.[2] Continued administration of the offending agent may worsen the reaction or induce desensitization. On the other hand, systemic reactions usually resolve in two weeks, with full recovery in four weeks, after the therapeutic agent is stopped.[3] The cholestatic form improves quickly after withdrawal of the drug, while the hepatocellular form resolves more slowly.[6] All fatalities have been of the hepatocellular or mixed type.[5,6] No evidence exists to indicate that preexisting liver disease increases the susceptibility to the hepatotoxicity of therapeutic drugs.[1]

Phenylbutazone may induce hepatitis by a hypersensitivity reaction in almost 1% of patients using it.[2] When its use is unavoidable, a complete blood count and liver function tests should be obtained before instituting treatment and at periodic intervals thereafter.[5] Slight elevations in tests of hepatic function can occur without significant liver damage developing, but progressive elevation should lead to cessation of phenylbutazone therapy.[2]

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Fracture Conference

Injuries of the Lower Cervical Spine

MIGUEL E. CABANELA, M.D.* and KENNETH A. JOHNSON, M.D.*

Dr. Miguel E. Cabanela:

This conference will concentrate on fractures of the lower cervical spinal column, that is, fractures from C-3 to C-7.

Case 1

A 16-year-old boy injured his cervical spinal column while wrestling. On falling to the ground, with his neck in an acutely flexed position, he immediately was unable to move his arms or legs. When seen in the emergency room, he had a complete paralysis, C-5 being the lower functioning level. There was no sensation to pain and temperature from C-5 distally, but he did have intact position and vibration as well as deep pain sensation. No other significant injuries were found.

Dr. Jim E. Crouse:

The anteroposterior roentgenogram shows an abnormality between C-5 and C-6 (Figure 1A), with narrowing of that interspace. The lateral view (Figure 1B) shows a dislocation of C-5 on C-6. With this much forward displacement, I would expect that there is a bilateral facet dislocation.

Dr. Cabanela:

What type of neurologic deficit does this patient show, and what is his prognosis for recovery?

Dr. Crouse:

The lesion is not complete and is called an anterior spinal cord syndrome. With such a partial lesion, the patient has a possibility of neurologic return, although it may not be complete.

Dr. Cabanela:

I agree. With the anterior spinal cord syndrome, if recovery starts to occur within 24 hours of the injury, the chances for complete or at least satisfactory recovery are good, but if there is no sign of recovery by 24 hours, the prognosis is worse. What should be done with this patient? It is now three hours after the injury.

Dr. Crouse:

I believe that the dislocation should be reduced to give him a better chance for a stable cervical spinal column as well as a better chance of neurologic recovery.

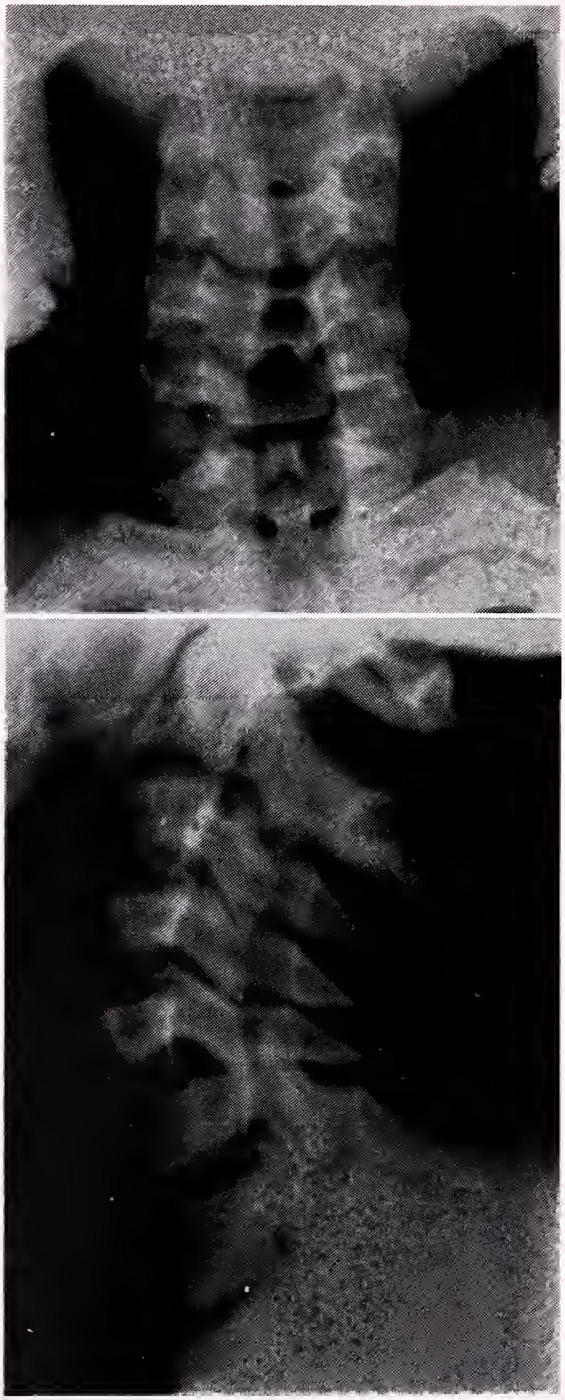

Fig. 1—(Case 1). Anteroposterior (A-top) and lateral (B-bottom) views on admission.

---

*Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Reprint address: Dr. M. E. Cabanela, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

Fracture Conference, July 28, 1976.

Dr. Cabanela: I agree. How would you reduce the dislocation?

Dr. Crouse:

The patient should be placed in halo traction with about 10 to 15 lb, weights should be added gradually, and serial roentgenograms should be taken to assess the reduction. Probably not more than 40 lb. should be used.

Dr. Cabanela: The halo traction was applied.

Dr. Mark B. Coventry:

Would you agree that an effort should be made to put the patient in traction with his neck flexed?

Dr. Cabanela:

Yes, the patient's neck was slightly flexed. Forty pounds of traction were needed to achieve reduction, and this roentgenogram shows the spinal column after the traction was reduced to only eight lb (Figure 2). At this point, it was approximately five hours after injury. The patient seems to have recovered some sensation to light touch and pain and has recovered a little motion of the toes and the fingers on one hand. Now what should be done?

Dr. Crouse:

I think that we should just wait and see what recovery occurs while the patient is in light traction.

Dr. Cabanela: Would you consider doing a fusion at this time?

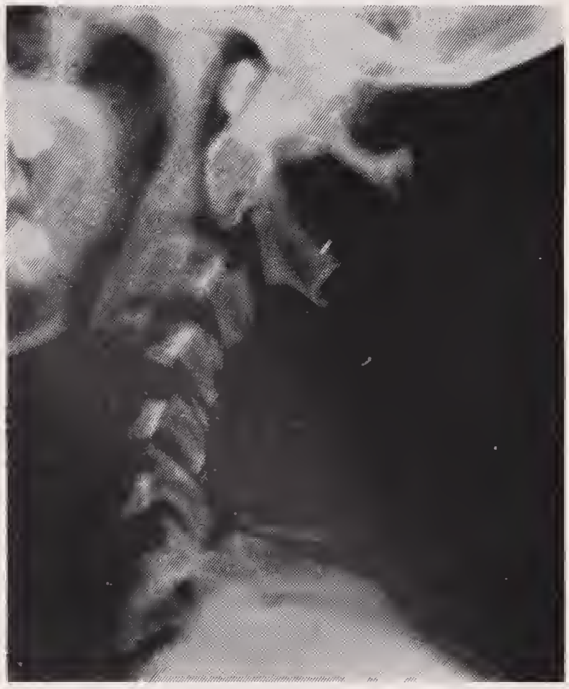

Fig. 2—(Case 1). Postreduction lateral view.

Dr. Crouse:

No, although a complete dislocation without associated fracture is less likely to heal than if a fracture was associated with it. I think that his cervical spinal column may become stable with time, and instead, I would favor halo cast immobilization.

Dr. Cabanela:

Forty-eight hours after injury, the patient showed definite neurologic recovery. He could move both legs and his right arm satisfactorily, but not his left arm. He had recovered sensation to light touch and pain.

He was placed in a halo cast approximately 8 days after injury, when he had approximately 75% recovery in his legs and right arm and 30% in his left arm. He was kept in the halo cast for 3 months, after which he had complete recovery of both legs and his right arm and 80% recovery of his left arm.

Schneider[1] was one of the first to describe this syndrome in 1955, and at that time, he recommended that an extensive laminectomy and section of the dentate ligaments be carried out for this type of problem. At present, this type of treatment is not recommended.

Well, at three months after injury, do you have any further suggestions for treatment?

Dr. Crouse:

The halo cast can be removed, and the stability of the cervical spinal column assessed.

Dr. Cabanela:

The patient was examined with fluoroscopic image-intensification (Figure 3), and with the patient's neck in flexion, it appeared that dislocation would recur. What should be done?

Dr. Crouse:

Because it is three months after the injury and his cervical spinal column is still unstable, I think that fusion should be considered.

Dr. Cabanela:

A posterior C-5 to C-6 fusion was carried out. Care was taken to avoid extending the fusion to levels above or below the unstable interspace. Four months later, flexion-extension views show that the fusion area was solid (Figure 4).

In retrospect, although the type of treatment was theoretically correct, one could make a point for early fusion in bilateral facet dislocations. These are purely ligamentous injuries, and ligamentous injuries have a higher tendency for late instability than do injuries to bone, that is, fracture. Therefore, an early fusion may have saved this patient three months of halo cast immobilization.

Dr. Coventry:

Reducing the dislocation by traction and extension of the neck is not always as successful as it was in this case. Would you have added rotation and extension in an effort to lock the facets if extension had not been successful?

Dr. Cabanela:

Yes. The next case shows unilateral facet dislocation in which rotation was necessary, in addition to extension and traction, to achieve reduction. In bilateral facet dislocation, the rotational component is not as important, and therefore, rotation does not have as significant a role in reduction.

Dr. Kenneth A. Johnson:

Do you think reducing the dislocation made any difference in his neurologic recovery?

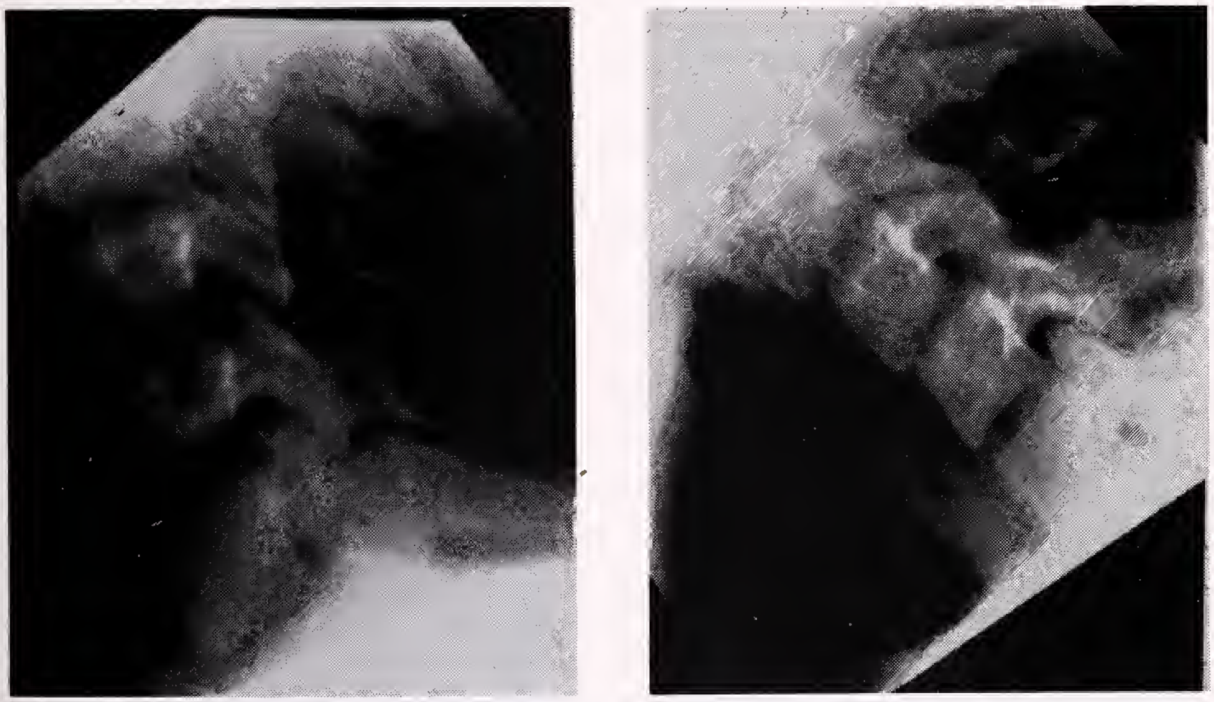

Fig. 3—(Case 1). Extension (A-left) and flexion (B-right) lateral views of C-5 and C-6 interspace taken three months after injury.

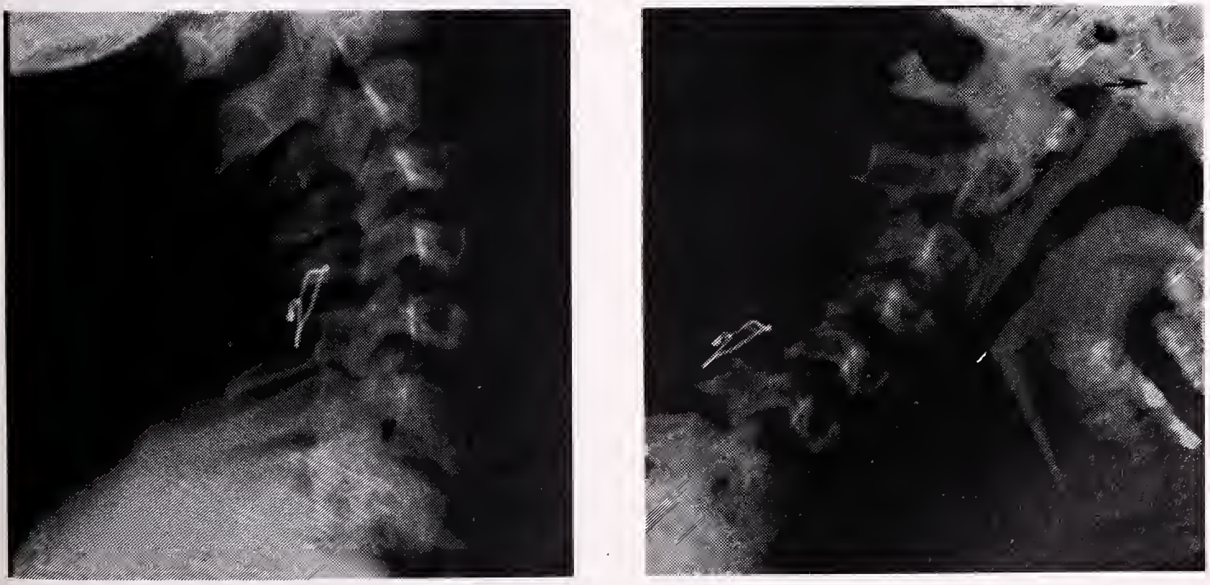

Fig. 4—(Case 1). Extension (A-left) and flexion (B-right) lateral views taken four months after posterior fusion.

Dr. Cabanela:

In this case, I have no doubt that reduction effected a decompression of his compressed anterior cord. However, the literature shows no definite evidence that, in general, reduction improves the neurologic prognosis. Perhaps the only exception is when the facet dislocation is unilateral and is accompanied by a radicular problem. If this happens, reduction improves the neurologic prognosis, at least for the recovery of a specific root. In this area of the spinal cord, one root level can make a great difference in the ultimate functional prognosis.

Dr. Richard N. Stauffer:

Should these patients be given anything to reduce the cord edema?

Dr. Cabanela:

We use dexamethasone routinely for this purpose, although there is no absolute evidence that it is effective.

Dr. Philip G. Perkins:

D. K. Evans of England has had a large experience with spinal injury, and he has found that 95% of patients, including those with either a unilateral or a bilateral facet dislocation and with or without fracture, experience spontaneous fusion anteriorly. Only 5% required fusion procedures.

Dr. Cabanela:

This has not been the general experience in this country. The incidence of spontaneous fusion after cervical injuries has varied from 30 to 60%, but none of the series reported has included strictly pure facet dislocations.

Case 2

A 23-year-old man was driving home one night when his car went off the road. Within six hours, he was extracted from the car and transported to the emergency room. Examination demonstrated that he had a complete neurologic deficit, both motor and sensory with no sacral sparing, from the level of C-6 distally. These roentgenograms were taken in the emergency room (Figure 5).

Dr. Edward M. Fitzgerald:

The lateral view shows a subluxation of the body of C-6 on C-7.

Dr. Cabanela:

The anteroposterior view shows that the distance between the spinous processes of C-6 and C-7 is increased. The lateral view reveals displacement of less than 50% of the width of the vertebral body. In 1963, in some studies on cadavers, Beatson[2] showed that, if the displacement of one vertebral body on the next is 50% or more of the anteroposterior width of the body, both facet joints are dislocated or fractured. And if displacement is less than 50% of the anteroposterior dimension of the body, the dislocation is unilateral. Therefore, our patient had a unilateral facet dislocation. This can be seen on oblique views, which show

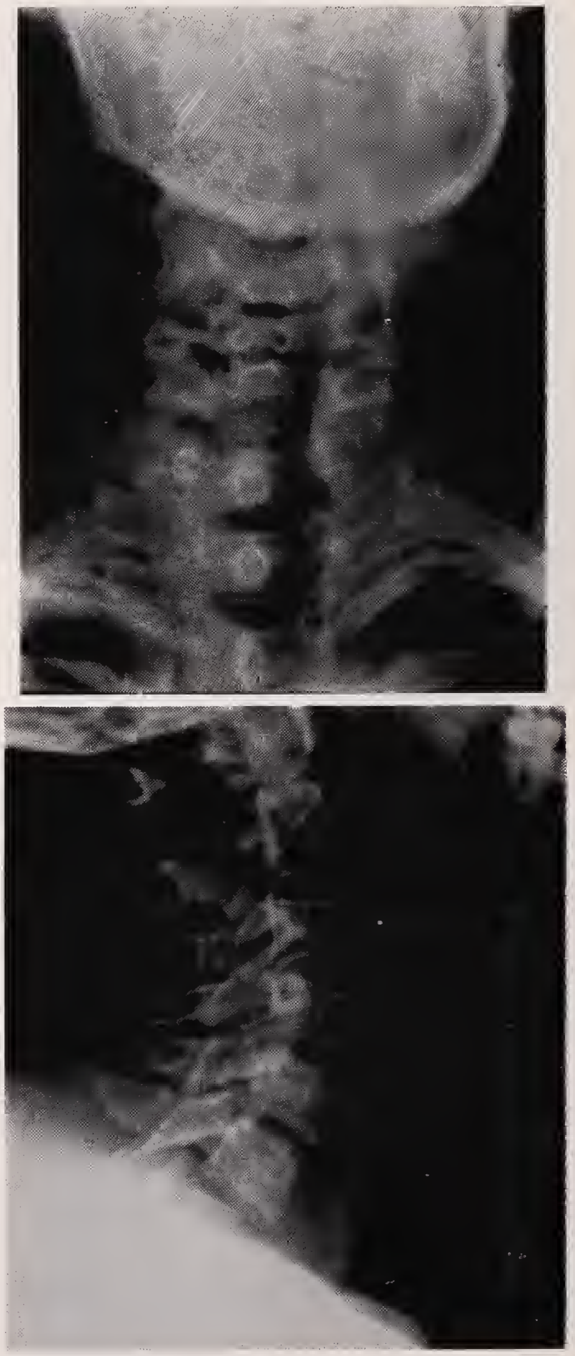

Fig. 5—(Case 2). Anteroposterior (A-top) and lateral (B-bottom) views on admission.

the dislocation on one side (Figure 6).

The patient had a complete neurologic deficit from C-6 distally, without sacral sparing. A halo device was applied in the emergency room. What should be done next?

Dr. Fitzgerald:

Traction should be used, with the patient's head in flexion, and an attempt at reducing the dislocation should be made.

Dr. Cabanela:

That was done. Without anesthesia, reduction was easy to accomplish with traction in flexion, then extension and slight rotation. After the reduction, both facets were reduced (Figure 7), but the distance between the spinous processes remained significantly increased. What should be done? It is now eight days after the injury. The patient's neurologic deficit remains complete, and he is in halo traction in a Foster frame.

Dr. Fitzgerald:

The chances for his recovery are now almost nil, and I think that a halo cast should be applied and physical therapy started.

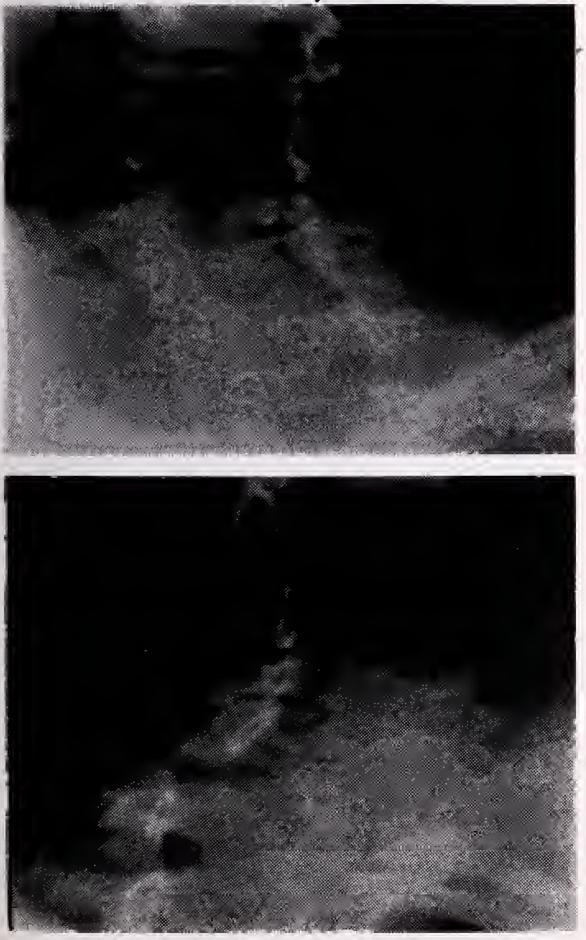

Fig. 6—(Case 2). Oblique views.

Dr. Cabanela:

Should there be concern about putting a halo cast on a patient who has no sensation?

Dr. Fitzgerald: Yes, because pressure ulcers may develop.

Dr. Cabanela:

The halo cast that was used was a very well-padded one. The patient was in a halo cast for six weeks, but from the third week on, he had skin problems, despite the adequate padding. At six weeks, the halo cast was removed. The patient refused to have another halo cast applied, and roentgenograms demonstrated persistent instability. Because of this, a posterior C-6 and C-7 fusion was done. The roentgenogram taken 9 weeks after fusion (Figure 8) shows not only posterior stabilization but also spontaneous anterior fusion. One could always argue that anterior stabilization would have occurred with or without the posterior fusion, perhaps if the patient had been kept rigidly immobilized for a longer time.

Dr. Rudolph A. Klassen:

Considering the problem of the halo cast with a complete neurologic loss, it does not have to descend down to the abdomen or iliac crest. A little vest is enough. These patients are primarily diaphragmatic breathers, and the abdomen should not be restricted.

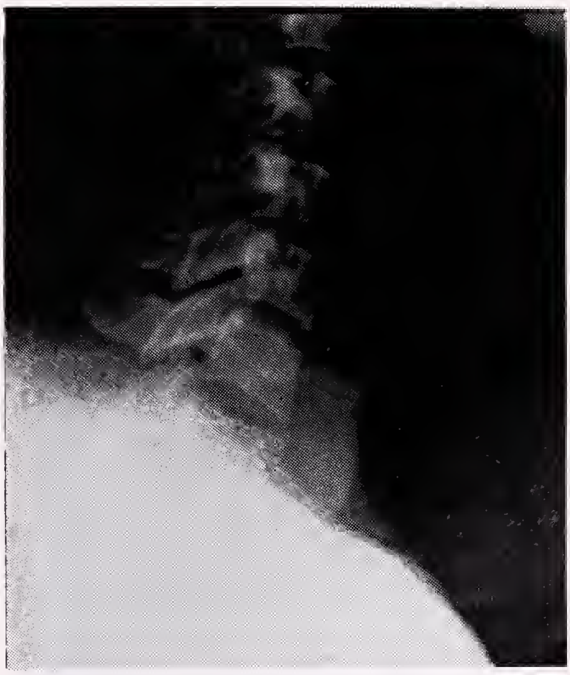

Fig. 7—(Case 2). Lateral view after reduction.

Also, because unilateral facet dislocations are fairly stable injuries, some of these need not be reduced, and healing will be satisfactory.

Dr. Richard S. Bryan:

Even though this is shown as a case of unilateral facet dislocation, with the amount of posterior disruption, could displacement have occurred on both sides?

Dr. Cabanela:

The initial roentgenograms show the resting situation after the energy of the trauma has dissipated. It is possible that, with the amount of disruption of the posterior elements and the serious neurologic deficit, the structural damage and displacement at the time of injury was far greater than that seen on the initial roentgenograms.

I wanted to show the contrast in these first two cases. No correlation can be found in the literature between the type of neurologic deficit and the type of structural cervical lesion. In general, bilateral facet dislocations are associated with greater neurologic damage than are unilateral facet dislocations. These two cases are exceptions, however.

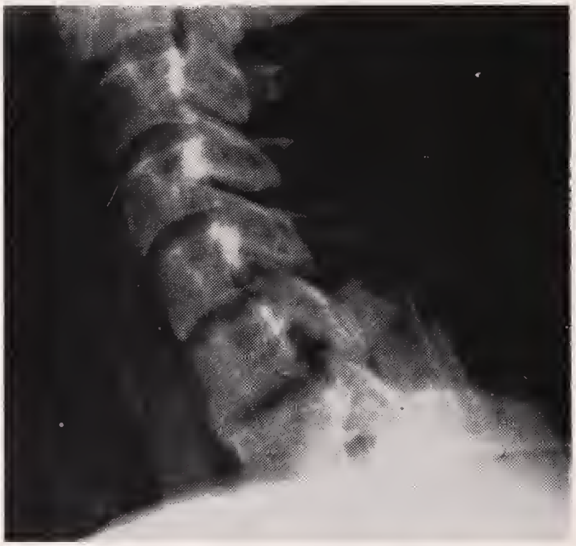

Fig. 8—(Case 2). Lateral view after fusion.

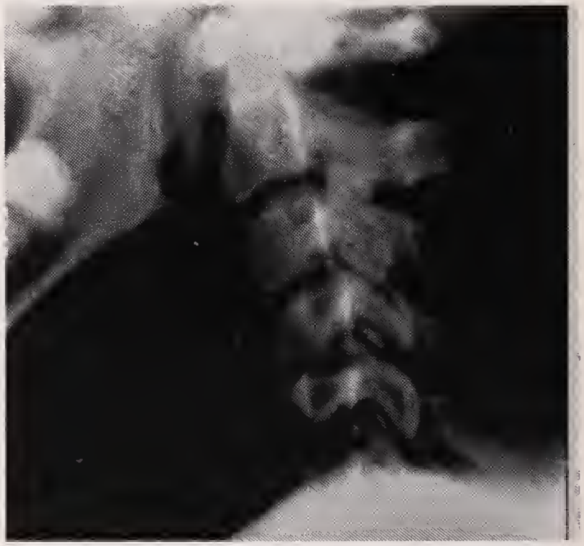

Fig. 9—(Case 3). Lateral cervical view on admission.

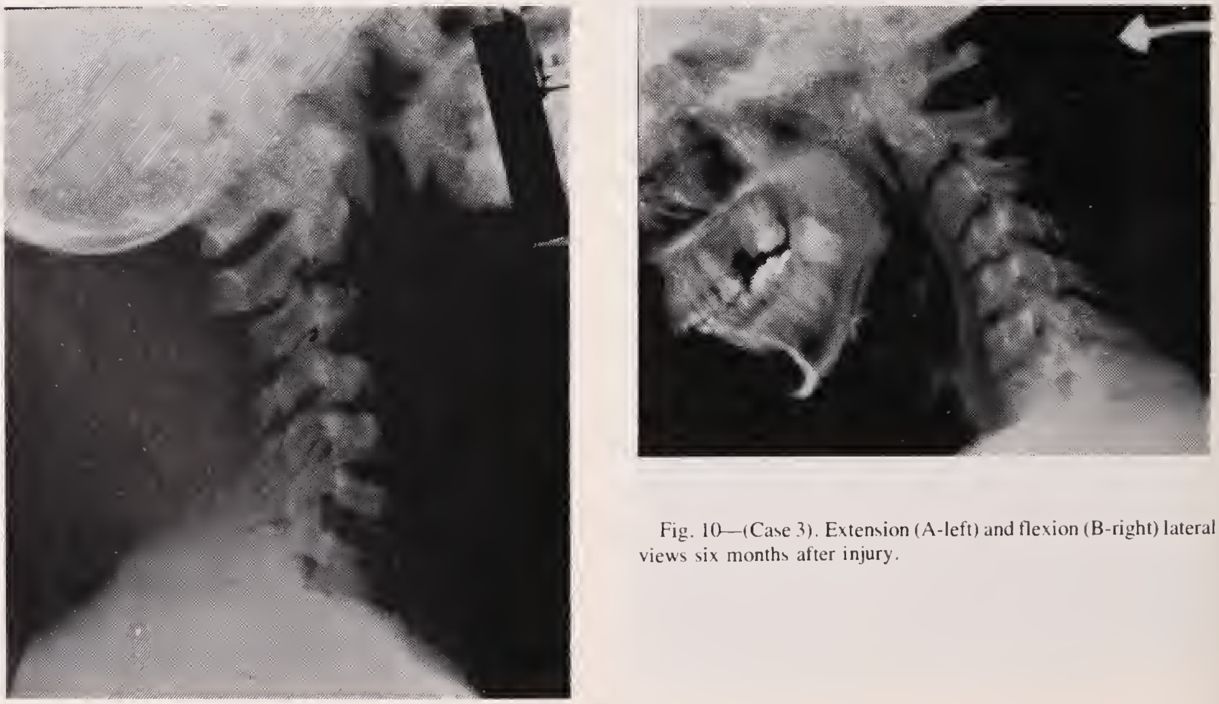

Fig. 10—(Case 3). Extension (A-left) and flexion (B-right) lateral views six months after injury.

Case 3

A 21-year-old man, while inebriated, dived into two feet of water and hit the bottom of the lake with the top of his head. He experienced immediate paralysis and could not get out of the water. He was rescued, however, and was brought to the emergency room within 30 minutes of the accident. There the patient had normal vital signs, was rather belligerent, and complained of neck pain. He had a C-5 quadriparesis. He had good rectal tone and perineal sensation. Involvement was significantly greater in the upper extremities than in the lower extremities. What type of neurologic deficit is there?

Dr. Elizabeth C. Quinlan:

There is an incomplete cord lesion. I am not certain what type.

Dr. Cabanela:

This is the central cord syndrome — another type of cord syndrome described by Schneider et al.[3] in the 1950s. It is unusual in this case because this syndrome is generally associated with extension lesions, commonly in a spondylitic spinal column, and this was a flexion lesion. Roentgenograms on admission (Figure 9) show a loss of cervical lordosis at the level of C-4 and C-5, and there is a fracture line vertically through the body of C-4. The anterior part of the body of C-4 is wedged. This is the so-called teardrop flexion fracture, and the mechanism of the injury is flexion and axial compression. This is one of the most vicious cervical injuries, and one that is likely to develop late anterior instability. The patient was placed in halo traction, and he started to recover neurologic function rapidly. He was kept in halo traction on a Foster frame for 2 weeks, at which time he had recovered enough lower extremity function to become ambulatory, and was placed in a halo cast. Roentgenographic appearance in the halo cast showed that the kyphosis at the fracture site persisted but this was accepted, and the patient was kept in a halo cast for three and a half months. During this time, neurologic recovery progressed, and at the end of this period, the patient had normal function of the left leg and left arm but had a slight residual neurologic deficit in his right arm and slight spasticity of the anterior musculature of his right leg.

This is another case of an incomplete lesion in which recovery was complete or almost complete with conservative treatment.

Dr. Klassen:

Interestingly, the patient did not achieve anterior bony union in three and a half months. This patient should be watched, because late instability may develop in this area.

Dr. Stauffer: That brings up the old problem of what is instability.

Dr. Cabanela:

According to Cheshire,[4] instability in a chronic situation is defined as abnormal motion in the sagittal plane that is seen between two vertebral bodies on roentgenograms of the spinal column taken in flexion and extension.

White et al.[5] stated that sagittal plane translation greater than 3.5 mm and sagittal plane rotation greater than 11° are ominous signs of instability. At 6 months, flexion and extension views showed that this patient's fracture was stable (Figure 10).

The central cord syndrome was described best by Schneider et al.[3] in the 1950s and is characterized by neurologic deficit that is more severe in the upper extremities than in the lower extremities. The lesion in the upper extremity is usually of the lower motor neuron type (flaccid), whereas the lesion in the lower extremity is of the upper motor neuron type (spastic). Usually, there is sacral sparing. The cause of the syndrome is either edema or hemorrhage in the central portion of the cord, and because the fibers of the lower extremities are more peripheral in the cord than are the fibers of the upper extremities, the damage to the upper extremities is usually greater than that to the lower extremities. Recovery occurs in the reverse order. Most commonly, this incomplete lesion occurs after extension injuries in patients with osteoarthritic spinal columns, although it has been noted in patients with normal roentgenographic findings, and also after flexion injuries in young patients. Pressure on the cord by the hypertrophic spurs or by bunching of the ligamenta flava has been implicated as the cause. Surgery is of no help, and the prognosis is relatively good. Commonly, there are some residuals in finger and hand function.

Only about 10% of cervical injuries require surgical stabilization. In most patients, the halo cast provides rigid immobilization while healing takes place.

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Rheumatology Corner

Role of Physical Medicine and Rehabilitation in the Care of Rheumatoid Arthritic Patients

MEHRSHEED SINAKI, M.D.*

THE PRINCIPLES of physical therapy and rehabilitation in the management of patients with rheumatoid arthritis are:

1. Adequate rest and a balance between the resting program and the exercise program.
2. A balanced diet for improving body resistance and avoidance of obesity which would later interfere with proper ambulatory activities.
3. Physical therapeutic measures for prevention of deformity, disuse atrophy and contractures, including patient education for effective use of the joints and muscles.

Since physical therapy for rheumatoid arthritis needs to be carried out daily and indefinitely, it is neither practical nor economical to have prolonged periods of professional therapy. The essentials of the physical therapy program are:

Thermotherapy: in the form of (1) An infrared lamp (250 watts) placed 18 to 22 inches from the skin and used once or twice daily for 20 to 35 minutes, (2) The infrared heat cradle or baker with 4 to 10 lamps for heating more extensive areas of the trunk and extremities, (3) Warm tub baths, 39°C (102.2°F) or a warm shower once or twice daily, and (4) Contrast baths which are useful for relieving morning stiffness of the hands and feet. For the latter two containers are used, one with hot water 42°-43°C (107° to 110°F), the other with cold water 18°-21°C (65° to 75°F). Hands or feet are immersed first in hot water for 10 minutes, then in cold water for one minute. From there on the hot water immersion is repeated for four minutes, and the cold water bath for one minute. The total duration for use of contrast baths is 30 minutes.

Other methods of heating which require hospitalization or treatment as an outpatient in a physical therapy facility include: Hubbard Tank at 38°C (101°F), whirlpool bath at 39°C (102.2°F) and deep heating methods (diathermy, ultrasound). The deep heating methods are useful in cases of chronic or subacute monoarthritis. They are contraindicated in the presence of joint effusion or acute flare-up of the arthritis involving multiple joints.

Massage, when applied properly, is effective in lessening edema and stiffness. Gentle massage may be applied daily in the form of stroking. Friction massage should be avoided in inflammatory arthritis except if the patient has scleroderma.

Therapeutic exercises: are of two types (1) Range of motion exercises. Here the purpose is to preserve the normal range of motion of the involved joints. These should be in the form of active or active assistive or passive exercises. (2) Resistive exercises. These are aimed to maintain power in muscles predisposed to weakness from disuse. Mild isometric strengthening exercises may be tried at home with 50 to 75% of maximal strength of the muscle. Modified resistive exercises can be performed manually or by lifting sandbags of light weight with few repetitions. If strengthening exercises increase joint effusion or pain, they should either be reduced or discontinued. Such exercises are avoided during the acute flare-ups.

Ambulatory activities: The importance of rest and avoidance of too much weight bearing on the affected joints of the lower extremities should be emphasized. Any exercise or activity causing increased pain, stiffness and swelling that persists beyond 24 hours should be modified. With the use of assistive devices, one can decrease weight-bearing on the lower extremities and continue with some ambulatory activities without causing damage to the affected joints. Proper shoes (such as plastazote or space shoes), application of T-bars or metatarsal pads or other appropriate shoe modifications might be helpful.

Occupational therapy: The occupational therapist can instruct the patient for energy conservation measures to avoid fatigue and damage to the affected joints. Proper splinting made of lightweight thermoplastic materials can be quite useful. The goals for splinting are: (a) To spare the joints from unnecessary trauma. (b) To prevent contractures and, in the case of hand splints, to avoid ulnar deviation deformities. (c) To provide comfort for the patient and induce resting of the involved joints without muscular disuse. (d) To decrease muscular co-contractions and misuse secondary to pain.

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Modifications of patient's bathroom facilities, such as application of grab bars at proper places and use of an elevated toilet seat, are important. It is important to have a proper bed at home with a hard mattress to prevent hip flexion contractures, not to forget proper positioning in bed with a thin pillow under the head, no pillow under the knees, and small pillows used for proper positioning of the affected shoulder in abduction to prevent development of shoulder adductor contractures. Application of proper supporting pads to the elbows over the rheumatoid nodules and heels help to prevent development of pressure sores in advanced cases.

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Malignancy of the Ovary – Campaigne (page 362).

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MMA Annual Meeting

RAMSEY COUNTY MEDICAL SOCIETY is hosting the 1979 MMA Annual Meeting. MMA President Dr. Robert Flom enthusiastically invites your attendance. He and his colleagues from St. Paul are anxious to welcome you May 16-17-18 at the Radisson St. Paul Hotel. Local Arrangements Chairman is Dr. John Burns. Scientific Exhibits are reviewed by Dr. Luigi Taddeini. Golf Tournament coordinators are Dr. Thomas Nichols and Dr. David W. Anderson. First Annual MMA Foot Races are planned by Dr. Edward Hanton and Dr. Lowell Lutter. Tennis Tournaments are under the direction of Dr. Leonard Levitan and Dr. Richard Graham. Preregister now and come to St. Paul for the 1979 MMA Annual Meeting.

The Minnesota Medical Association House of Delegates will meet Wednesday, May 16 and Friday, May 18 in St. Paul, Minnesota during the 1979 Annual Meeting of the MMA. Included on the agenda are Dr. Hoyt Gardner, Louisville, Kentucky, President-Elect of the American Medical Association, and Dr. George Pettersen, Minnesota Commissioner of Health. A major item to be considered by the delegates will be a report from the Commission on Health Care Costs of the Minnesota Medical Association.

Review

Malignancy of the Ovary

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*Duluth, Minnesota

Ovarian malignancy ranks as the fourth most frequent cause of death from cancer in women, and remains the leading cause of gynecologic cancer death. Approximately 10,000 new cases of ovarian cancer are diagnosed each year in the United States of which 70% will eventually be fatal. A community study of ovarian cancer was conducted in Duluth, Minnesota from 1960 thru 1975, and the results are presented as follows.

CARCINOMA OF THE ovary is the fourth most frequent fatal malignancy in women. It is estimated that there are 5,000 to 10,000 new cases diagnosed each year in the United States, of which 70% will be fatal.[1] Ovarian malignancy is responsible for a death rate greater than the death rates of uterine body and cervical neoplasms combined, making it the leading cause of gynecologic demise. There has been no change in the incidence of cancer of the ovary since 1947.[2] In the annual age adjusted mortality rates, Denmark leads the world with 11/100,000 deaths, and Japan the least number with 1.6/100,000. The mortality rate in the United States is 6/100,000[3] The most common ovarian cancer in the United States according to the Connecticut Tumor Registry from 1960-1964 is the serous cystadenocarcinoma comprising slightly more than 50% of the primary cases.[4]

Method

The medical records of the three Duluth Hospitals — St. Luke's, St. Mary's, and Miller-Dwan — were employed to determine all cases of primary and secondary pelvic cancer for the years 1960 through 1975. Carcinoma of the cervix accounted for almost two-thirds of the total, and cancer of the uterine corpus for 24.5%. There were 340 cases of ovarian malignancy or 14% of the total, as shown in Table 1.

In 55 patients (16.2%) of the 340 cases, involvement of the ovary occurred secondarily to malignancy occurring elsewhere (Figure 1).

The 285 cases of primary ovarian cancer were classified according to the system proposed by the International Federation of Gynecology and Obstetrics (FIGO)[5] utilizing the clinical description, the surgeons' operative report, and the pathology reports.

An attempt was made to determine survival rates by utilizing the records of the Duluth Tumor Board. Data was available in 92% of all cases with primary ovarian malignancy, from the minimum post treatment period of one year to maximum follow-up period of five years. The actual calculation of survival rates was based on the direct or ad-hoc method[6] rather than the actuarial method because of the small number of cases in this study.

Age Distribution

With reference to age distribution, one can observe (Table 2) the average age is 56.4 years, the median age

TABLE 1
Distribution of Ovarian Cancer
St. Luke's, St. Mary's, Miller-Dwan Hospitals
1960-1975

Primary Cases	285	83.8%
Secondary Cases	55	16.2%
Total	340	100 %

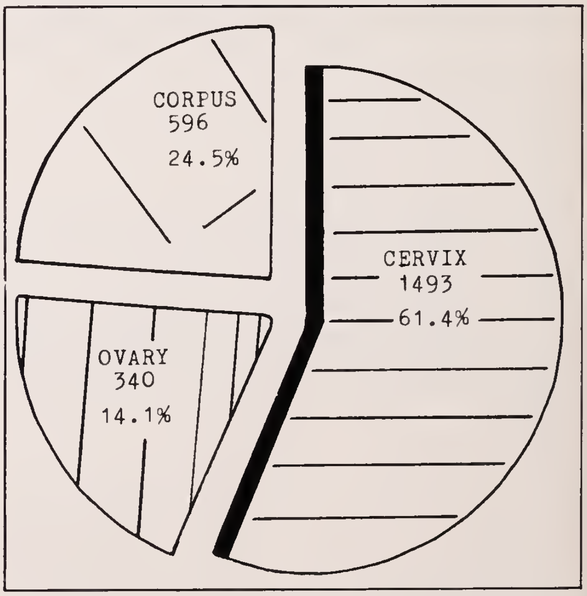

Fig. 1 — Distribution of Pelvic Cancer St. Lukes, St. Marys, Miller-Dwan Hospitals, 1960-1975.

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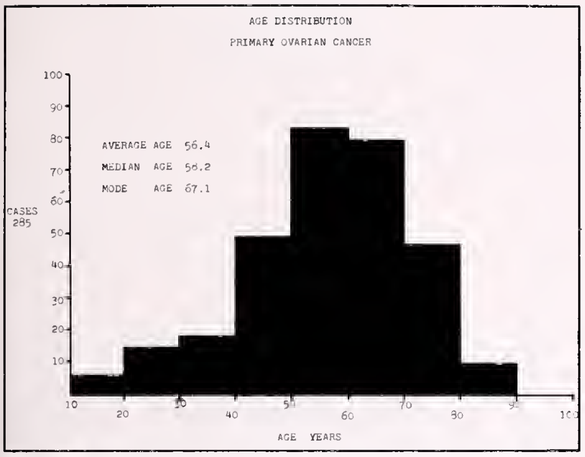
*Duluth, Minnesota.
*See editorial, page 335.

TABLE 2



is 58.2 years, and the mode is 67.1 years. The youngest patient was a 14-year-old white nulliparous female with a serous cystadenocarcinoma, the oldest case that of a nulliparous 90-year-old white female also with a serous cystadenocarcinoma. Both cases were fatal within one year of diagnosis. The age distribution conforms fairly well with the Roswell Park Study.[7]

Symptomatology

Cases of primary ovarian cancer presented with three consistent symptoms: pelvic pain, mass, and abdominal distention. If vaginal bleeding was included as a fourth initial symptom, over 90% of the cases could be diagnosed clinically.

Type and Extent of Primary Ovarian Cancer

In this study, undifferentiated adenocarcinoma was the most common variety, comprising almost one-third of the total cases. Serous cystadenocarcinoma, the most prevalent primary ovarian malignancy in review of the American literature[3] amounted to only 13.4% of the total. Malignancies of the stroma and germ cells amounted to less than 10% of the total cases. This variation in the types of malignancies may in part be due to the older age group in this series, wherein epithelial malignancies tend to predominate. The types of malignancy are seen in Table 3.

TABLE 3
Classification of Primary Ovarian Neoplasms

Types	Cases	
1. Undifferentiated Carcinoma	92	32.2%
2. Papillary Cystadenocarcinoma	42	14.8%
3. Papillary Adenocarcinoma	40	14.1%
4. Serous-Cystadenocarcinoma	38	13.4%
5. Mucinous Cystadenocarcinoma	35	12.3%
6. Granulosa Cell Tumor	8	2.8%
7. Clear Cell Carcinoma	8	2.8%
8. Dysgerminoma (Seminoma)	5	1.7%
9. Teratoma	4	1.4%
10. Others, thecoma, arrhenoblastoma etc.	13	4.5%
Total Cases	285	100%

Each case was further classified according to the F.I.G.O. system of five categories: Stage I, growth limited to the ovaries; Stage II, growth involving one or both ovaries with pelvic extension; Stage III, growth with widespread intraperitoneal metastases; Stage IV, growth with distant metastases; and Stage V, unexplored cases thought to be ovarian cancer. Table 4 demonstrates the distribution of the cases in this report. Only 31.5% of the cases were limited to the ovaries at laparotomy while advanced disease was present in 68.5% of all patients.

TABLE 4
F.I.G.O Stagegrouping for Primary Cancer of the Ovary

Stage 1.	Growth Limited to the Ovaries	90 Cases	31.5%
1a	Growth limited to one ovary no ascites		45
1b	Growth limited to both ovaries no ascites		18
1c	Growth limited to one or two ovaries with ascites and malignant cells		27
Stage 2.	Growth Involving Ovary (s) with Pelvic Extension	47 Cases	16.5%
2a	Extension to uterus, tubes, or other ovary		6
2b	Extension to other pelvic tissue		41
Stage 3.	Growth Involving Ovary (s) with Widespread Intraperitoneal mets.	72 Cases	25.3%
Stage 4.	Growth Involving Ovary (s) with Distant mets.	70 Cases	24.5%
Stage 5.	Unexplored Cases	6 Cases	2.2%
	Total Cases	285	100%

Treatment

Traditionally, surgical therapy has been the cornerstone in the management of ovarian malignancy. In this series, for Stage I ovarian cancer, total abdominal hysterectomy, bilateral salpingo-oophorectomy with omentectomy was the primary treatment in 50 cases (55.5%). The above surgery combined with x-ray therapy of 2900-3450 rads to the pelvis was utilized in 31 cases (34.4%). Unilateral oophorectomy was performed in four cases (10.1%) because of nulliparity.

In Stage II ovarian cancer, the modality of treatment was total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy, combined with x-ray therapy of 2900-3450 rads in 30 cases (63.9%). Seventeen cases (36.1%) were treated with surgery and chemotherapy in the form of Cycophosphamide (Cytoxan), or Chlorambucil (Leukeran) and l-phenylalanine nitrogen mustard (Alkeran).

For Stage III ovarian cancer, the major effort was "debulking" of the malignancy, followed by x-ray therapy, and then long term chemotherapy. Abdominal hysterectomy with bilateral oophorectomy, and removal of as much metastatic tumor as possible was performed in 30 cases (41.6%). In 42 cases (58.4%) only biopsy of the tumor was performed, followed by x-ray therapy and/or chemotherapy.

In 70 cases (100%) of Stage IV ovarian cancer, surgery was limited to biopsy only followed by x-ray therapy in 34 cases (48.5%) and chemotherapy in 36 cases (51.5%). With massive abdominal effusions, Colloidal AU^{198} or chromic phosphate $PO4^{32}$ was utilized in 18 cases post-operatively.

Survival

Figure 2 demonstrates the survival rates of all types of primary malignancy of the ovary. The determination was done on an annual basis, in all categories. The survival rates correspond fairly well with Parker's series.[8] 50% of all cases of Stage I cancer were alive at five years. 19% of the patients in the Stage II category survived 5 years, and 10% of the cases in Stage III. There was one patient that survived with Stage IV cancer of the ovary in the five year period.

Discussion

Interestingly, over 90% of the secondary cases of ovarian malignancy originated in the stomach, breast, colon or pancreas, indicating the necessity of a thorough work-up in all cases of pelvic mass suspicious for neoplasia. There were 28 cases (12% of the total) of primary ovarian cancer having had previous hysterectomies for benign disease which may suggest the need of prophylactic oophorectomy at the time of hysterectomy. Nine cases (3.9% of the total) experienced a malignancy of the breast prior to the development of the second primary lesion in the ovary. There is twice the incident risk of subsequently developing a separate primary cancer of the ovary in women having had a cancer of the breast.[8]

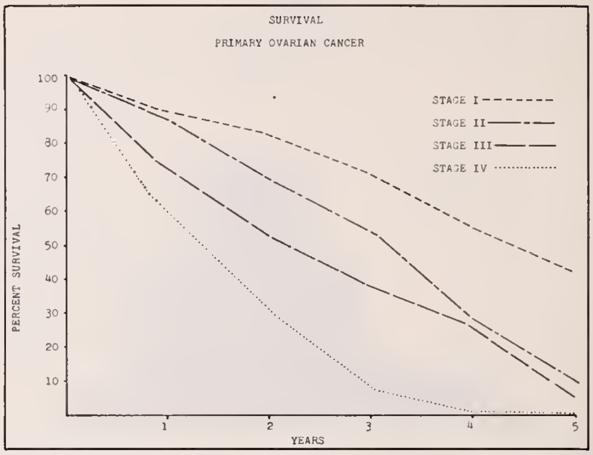


Figure 2

Two patients were pregnant at the time of unilateral salpingo-oophorectomy for Stage IA cancer, both with mucinous cystadenocarcinoma. The pregnancies terminated normally. Abdominal hysterectomy and contralateral salpingo-oophorectomy were subsequently performed. In both cases, microscopic metastases were observed in the ovaries removed at the time of hysterectomy, suggesting the necessity of abdominal hysterectomy and bilateral salpingo-oophorectomy in Stages IA and IB as stressed by Richford et al.[10]

Summary

With the vast majority of the cases of primary ovarian cancer beyond the confines of the pelvis at initial laparotomy, more aggressive surgery in the form of "debulkment" in addition to hysterectomy and bilateral salpingo-oophorectomy is becoming more popular. In the contemporary scene, surgery is followed by more intensive adjuvant chemotherapy.[10,11] Combination chemotherapy, less costly, more convenient, with fewer complications appears to be supplanting x-ray therapy as the primary adjuvant to surgery.

The management of ovarian cancer demands more than one modality of treatment regardless of the extent of the disease. At present, it requires the combined efforts of the surgeon, chemotherapist, and radiologist.

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7-12. Will be found on page 359.

Legislation

Minnesota "Brain Death" Legislation: A Step Forward . . . Or Backward?

JOHN S. HAMLON, M.A.* and JOHN M. BURNS, M.D.†

II. Defining "Brain Death."

Introduction

Since Kansas first enacted "brain death" legislation in 1970, over one-third of the United States has followed suit with varying legal definitions of death. With the advantage of hindsight, many of these states tried to formulate "air-tight" definitions of death based on constructive criticisms of preceding legislative enactments. However, the search for the "perfect" definition of death still goes on as physicians, lawyers, theologians, philosophers, and persons-on-the-street continue to add their respective insights to the "brain death" dialectic.

The main statutory objective has been to get across the *concept* of "brain death" while avoiding definitional criteria which could make the statute, itself, susceptible to change were "better" criteria discovered in the future. But conceptualizing death in legal terms *has* involved the use of certain criteria ("irreversible cessation," "total," "functioning," etc.), since it is obviously insufficient to say "the concept of 'brain death' is correct and legal." A substantial part of the "brain death" debate, then, centers around these criteria, however carefully and concisely formulated. Indeed, the very concise and general nature of these criteria has raised the question, "Can and will such criteria be misinterpreted?"

There are, of course, different ideas of what constitutes a "perfect" definition of death. For some, a "perfect" definition will stress *permanent loss of consciousness* rather than "*total* brain death."[1] For others, it will *exclude* any interpretative allowance for passive or active euthanasia.[2] Again, for some it will reflect solely the public's desire within each respective state, whereas for others it will reflect a nation-wide consensus of opinion.[3]

A "perfect" definition would exclude the allowance for enthanasia by: (1) eliminating any confusion between total brain death and lesser degrees of extensive brain damage and (2) being so "perfectly worded" as to preclude the possibility of future improvement or any intention to broaden the scope of the death pronouncement.[2]

A Comparison of Two Definitions

Within the last few years, two separate groups have attempted to offer the public a legal and universally acceptable definition of death. On February 24, 1975, the American Bar Association — after two and a half years of study and formulation — offered the following definition:

> For all legal purposes, a human body with irreversible cessation of total brain function, according to usual and customary standards of medical practice, shall be considered dead.

Some three years later, the National Conference of Commissioners on Uniform State Laws drafted the "Uniform Brain Death Act:"

> For legal and medical purposes, an individual who has sustained irreversible cessation of all functioning of the brain, including the brain stem, is dead. A determination of death under this section must be made in accordance with reasonable medical standards.

Despite the availability and stated advantages of the American Bar Association definition, including "avoidance of passive and active euthanasia,"[4] the National Conference of Commissioners eventually chose terms and phrases more open to interpretation . . . and criticism.

Soon after its adoption, McCarthy DeMere, a lawyer-doctor and the American Bar Association's advisor to the National Conference of Commissioners on Uniform State Laws, critiqued the "Uniform Brain Death Act," showing its vulnerability to misinterpretation and modification. His critique is paraphrased and quoted here as an example of how crucial semantics are in such a definition.

According to DeMere, the title "Uniform Brain Death Act" (as opposed to his recommended title, "Uniform Definition of Death Act") creates an ambiguity in both legal and medical professions whereby "brain death" and death of the heart or lungs are seen as separate entities.[5]

Regarding the proposed Act itself, DeMere sees several difficulties in the wording:

> 1. Regarding the phrase "for legal and *medical* purposes," he would eliminate the word "medical" because "no Law should be enacted giving medical purposes. All that is needed is a Law for all legal purposes."

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2. DeMere prefers "human body" to "individual" because the latter word can refer to any animate or inanimate object. (He also objects to the word "person" since, by legal process, a corporation can be termed a "person.")

3. A more substantial objection is found in the phrase "irreversible cessation of all functioning of the brain." To DeMere, there is a vast difference between "functioning of the brain" and "brain function." The main "function" of the brain is to survive, since it is the only organ in the body that does not reproduce its cells.

Secondary and tertiary *functions* of the brain are synonymous, says DeMere, with brain *functioning*. The brain's secondary function is to conduct electricity, and its tertiary function includes all the activities of the brain such as "moving, thinking, and sensing being a person or individual." (In other words, if the phrase "including the brain stem" were eliminated, one could interpret "all functioning of the brain" to cover only the secondary and tertiary functions.)

4. DeMere prefers "shall be considered dead" to "is dead." "It is too strong to state, 'is dead,' " says DeMere, "when we know that medicine is an art and not a science. Therefore, 'shall be considered dead' is in deference to the pronouncement of death by medical standards."

5. In DeMere's opinion, the last phrase, "in accordance with reasonable medical standards," will be strongly opposed by the medical profession. He feels that such a statement works a hardship on the medical profession because what is "usual and customary" in medical practice might not be synonymous with what a court of law deems "reasonable." He cites the case of a young woman, under forty, who sued her physician because he had not tested her eyes for glaucoma, the cause of her developing blindness. Whereas the physician stated that it was not "usual and customary" to do routine tonometry examinations on individuals under forty, the court decreed that it should have been "reasonable" to do tonometry on all individuals. "It is very easy to see," says DeMere, "that the courts can interfere very strongly with the pronouncement of death by setting reasonable, medical standards, when it is up to the medical profession to maintain stringent, current, 'usual and customary' standards of medical practice."

6. In the "Comment" section of the "Uniform Brain Death Act," it states that the critical word "functioning" expresses the "idea of *purposeful* activity in all parts of the brain organ, as distinguished from random activity." DeMere believes that this statement, by itself, will be intolerable to Right to Life groups (presumably since it could serve as a verbal wedge to open the door for passive or active euthanasia).[6]

Although several of DeMere's criticisms center around minor flaws, we agree with him that the Uniform Brain Death Act, along with its Prefatory Note and Comment, has a certain ambiguous flavor that lends itself to serious misinterpretation as well as contention.

Especially is this true of the Prefatory Note, where it states

> . . . That technology creates a concern among medical practitioners that legal liability might be imposed when life-support systems are withdrawn, even though the case is *hopeless* (emphasis ours) and acceptable medical practice sanctions the withdrawal[13]. . . .

The word "hopeless" is wide open to interpretation: Does it here describe the state of an actual "brain dead" body or the determination of an irreversible *process* towards "brain death?"

It is interesting to note that the National Conference of Commissioners had ample opportunity to draw upon the hard-earned drafting experience of the ABA as well as numerous constructive criticisms of existing state definitions and yet came up with an Act that the ABA and much of the medical community may not comfortably accept.

If nothing else, a study of these two attempts to draft a universally acceptable definition of death should alert us to the fact that (1) hindsight does not automatically ensure better law, (2) a definition of death can have the potential for causing more problems than it was designed to solve, and (3) it is not that simple to find exact words to legally convey the phenomenon of death.

How Definitive Should a "Brain Death" Definition Be?

But even if the ABA definition is in fact, superior to the "Uniform Brain Death Act," is it definitive enough to separate those actually "brain dead" from those who simply appear so? Does the ABA definition effectively truncate all intentional or unintentional moves to interpret "brain death" as simply the irreversible loss of neocortical function?

Philosophers Germain Grisez and Joseph Boyle feel that no presently existing "brain death" definition, including the ABA definition, goes far enough to unequivocally spell out its presumed intention to protect each individual from the possible injustice of being prematurely declared dead. For example, in Chapter Three of their recently published book, *Life and Death with Liberty and Justice: A Contribution to the Euthanasia Debate,* Grisez and Boyle zero in on DeMere's explanation of the phrase "usual and customary standards of medical practice." DeMere states in the report of the ABA's Committee on Medicine and Law that this phrase covers

> . . . the situation where the standards are even different in the same hospital. In the intensive care unit the standard of medical practice of the pronouncement of death could be the 'lack of brain waves by the electroencephalogram' (In other parts of the hospital other appropriate standards would be used.)[7]

Grisez and Boyle point out that

> Since EEG *cannot* by itself evidence lack of function of the entire brain . . . DeMere's exegesis of "usual and customary standards of medical practice" is a substantial cause for concern that the way is being paved to set new boundaries of legal personhood, and in this way to deprive some persons of all their rights,

without facing up to the fact that this is what is being done.[8]

Grisez and Boyle strongly feel that "if death can be correctly defined in factual terms as the complete and irreversible loss of the functioning of the entire brain," then such a definition can be "translated into operational and legal terms without any radical shifts in meaning, arbitrary stipulations, or subjective evaluations."[9]

Translating a factual definition of death into appropriate statutory terms would, for them, involve five codifiable areas:

> 1. A definition of death stated in "theoretical and factual terms," which would (a) "make clear that all deaths are events of a single kind" and (b) include operational criteria clearly signifying the occurrence of death in those terms.
> 2. A statement on the "degree of certitude necessary in judging that death has occurred, in order to prevent injustice to those who seem to be dead but are in fact alive."
> 3. A statement on the "criteria and procedure for judging death in ordinary cases."
> 4. A statement on the "criteria and procedures for death in extraordinary cases" which would "regulate the activity of physicians to ensure that injustice is not done to anybody." (They point out that the "careful regulation of the activity of physicians does not imply that the law considers every physician to be under suspicion, but only implies that the law cannot consider every physician to be altogether above suspicion.")
> 5. A statement that this definition of death does not "effect existing legal provisions concerning the presumption of death in the absence of an individual presumed dead."[10]

Along with explanations of and justifications for each of these five areas, Grisez and Boyle offer corresponding statutory statements for future legislative consideration. For example, in the first codifiable area where death is defined in "theoretical and factual terms," they propose the following:

> Death is the permanent termination of the integrated functioning characteristic of a living body as a whole. In human individuals beyond the embryonic stage of development, death occurs when there is a complete and irreversible loss of the functioning of the entire brain.[11]

In this definition, one immediately notices a difference in thrust from that of the ABA definition and the "Uniform Brain Death Act:" Whereas the latter two contain the respective pronouncement statements, "shall be considered dead" and "is dead," Grisez and Boyle's definition simply *defines,* leaving it to the physician to "consider" or "pronounce."

By adding four other "parts" to this basic definition of death, Grisez and Boyle are, in effect, challenging the notion that a *concise* definition of death can be drafted with no interpretive loopholes. The distinct advantage of an expanded definition, such as theirs, is that the intention behind it can be spelled out. In their definition, Grisez and Boyle leave no doubt that they wish to protect the rights of the individual who is not actually "brain dead."

If the Minnesota legislature opts to statutorily define death, then Grisez and Boyle's proposal presents an alternative that should be studied carefully. However, given the push to get a legal definition on the books, we wonder whether there will be time to digest their ideas, as well as others that will surface as more physicians, lawyers, theologians, and philosophers take a second and third look at the complex problem of defining death.

Summary

This brings us back to the importance of the educative process, which takes time. Whether or not the Minnesota legislature eventually defines death, it is our opinion that a vital educative process regarding "brain death" is still going on, and that a "brain death" definition during the present Minnesota legislative session would be premature, if for no other reason than this learning process is not complete. Perhaps even Grisez and Boyle's proposal will be refined when there has been time to digest and constructively criticize what they are saying. Or perhaps, in time, the medical and legal professions will come to a better mutual understanding of their respective problems and responsibilities, obviating the present, expressed "need" for "brain death" legislation.

Meanwhile, as many correctly suggest, there *is* a present need in Minnesota to understand and accept the concept of "brain death" in order to alleviate undue litigative pressure, real or imagined, on the conscientious and concerned physician. For instance, there is some reluctance on the part of Minnesota transplant harvesting teams to a keep a "brain dead" body profused (the heart beating, etc.) for the purpose of removing organs under ideal circumstances. This reluctance stems from the fear of litigation in the case of the heart-beating cadaver, where a profused organ is removed *before* the termination of artificial support systems in order to ensure optimal organ-graft survival.*

Many believe that this medical "wariness" can be solved once and for all by legislating a correct defintion of death. However, by comparing the ABA definition of death with the "Uniform Brain Death Act" and briefly introducing Grisez and Boyle's proposal, we have attempted to show that "justly and correctly" defining death is neither a simple nor necessarily a finished process. We would hope, therefore, that the Minnesota legislature would defer a decision on "brain death" until more essential data and dialogue are exchanged between the professions most directly affected, namely the medical and legal professions.

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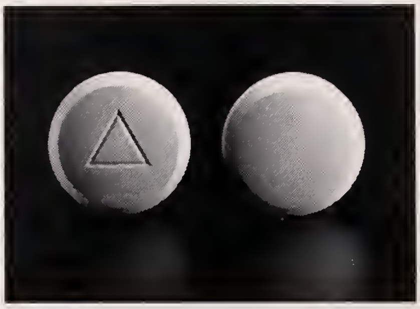
*With regard to the necessity for brain death prior to kidney harvest, at the present time it is rare to exchange kidneys between various centers when the kidneys have not been taken from a heart-beating cadaver. Perhaps, in rare occasions, a transplant center may use kidneys which they have harvested from a patient who had complete cardiac arrest with rapid retrieval, but the past experience with such attempts has been unsatisfactory. Acute tubular necrosis, cortical necrosis, and technical problems with the retrieval all led to more difficult post-transplant care and results which were not as good as those kidneys which were perfused up until the time of retrieval.[12]

References will be found on page 372.

The Make

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to
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literature on this sub
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MYTH: Industry favor
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FACT: PMA compan
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T: About 55 percent
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H: Generic
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g consumers large
of money.

T: Market data show
you invariably
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s the patient receives
ven brand product.
ngs from voluntary
andated generic
cribing are grossly
gerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

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History

Infanticide

A Historical Perspective

BEVERLY A. MONTAG, B.S. MED. TECH., M.P.H.* and THOMAS W. MONTAG, M.D.†

The practice of infanticide has prevailed among many countries and cultures of the world sometime in their history. This article reviews some of the reasons that infanticide occurred in pre-history and how this phenomenon has come down even into the 20th century in some cultures. The article also discusses how society has changed its attitudes toward infanticide, how legislation has attempted to control infanticide, and how this phenomenon still exists in our society in the form of child abuse.

THE PURPOSE of this paper is to review for the physician and other health professionals the historical occurrence of infanticide in western culture. Infanticide is defined as the willful killing of a child between birth and one year of age. This differentiates it from both abortion and filicide. Abortion, considered by some to be a form of infanticide, is one of today's polemical issues. Technically abortion is not infanticide as it deals with death before birth. Filicide deals with a parent killing his/her own child, usually over a year of age. In all probability written history does not reflect the true magnitude of infanticide, but it does acknowledge the presence of the practice.

Early History
(7000 BC to 300 BC)

Infanticide has been practiced since prehistoric times. Children have been thrown into rivers and burning pits, "potted" in jars to starve to death, exposed on hillsides and in streets, suffocated, mutilated, and beaten to death. Bones of infants dug up by archeologists, with inscriptions identifying them as first born sons of noble families, date all the way back to Jericho of 7,000 B.C. Hiel the Bethelite built Jericho with his youngest son interred in the gates and his firstborn son buried under the foundation. Indeed, sealing children in wells, foundations, and bridges to strengthen their structure was common from the wall of Jericho to Germany in 1843.[1] Children were immured in the dykes of Oldenburg until the 1600s. Archeologists have found jars containing bones of infants of Canaanites buried under house corners, thresholds, and floors.

Child sacrifice has been practiced in many ancient cultures to avert evil and purchase good. It was performed by the Irish Colts, Gauls, the Scandinavians, the Egyptians, Phoenicians, Meabites, and Ammenites. The Jewish King Manasseh sacrificed his son to the god Molech. Carthaginian child sacrifice is well documented. Parents willingly offered up their own children. It was an honor for parents with only one child to sacrifice that one infant. Childless couples would purchase children from poor peoples and offer these children for sacrifice. Parents of sold children were not permitted to shed tears. If they did, payment was forfeited and the child was killed anyway.

The Vikings had a ritual which in essence determined the fate of newborns. The father extended a spear to newborn boys. If the child seized the handle he was allowed to live. Among other Scandinavians the newborn infant was placed on the ground in front of the father. If the father did not take the child into his arms, it was killed. The father was allowed to expose his child (a form of abandonment) to take revenge for an insult from his wife. A brother could kill the child of his sister if its birth resulted in death of the mother.

Ancient Greece and Rome

In the Grecian states of old infanticide was not only permitted but enforced by law. A Spartan lawgiver decreed that all infants be examined by the older men of the community. If found to be deformed or weak the child was thrown into a deep cavern at the foot of Mount Taygetus, "concluding that its life could be of no advantage to itself or to the public."[2] The practice was defended by Aristotle and Plato as a means of getting rid of deformed children and preventing an excess of population. Infanticide in Athens was rendered easier because the child was not considered a

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full human being until a ceremony, called Amphidromia, was performed. Before the ceremony the child could be freely exposed. Such exposure meant that death was the most merciful fate to befall it. Often, however, the child would be picked up and reared for slavery and prostitution. Aristippus, a Greek philosopher, asserted that man can do what he wants with children (an attitude still prevalent today).

In Rome fathers were invested with absolute authority over the lives and fortunes of their children. Infanticide and exposure were common practices. In the Law of Twelve Tables, Romulus gave unqualified jurisdiction to the father for destruction of all deformed children after exhibition to and consent from five neighbors. Pliny the Elder condoned rights of parents to destroy children to preserve proper population.

Impact of Judeo-Christian Values

Allusions to infanticide are quite common in the Bible. The Pharaohs commissioned midwives to murder all male offspring of Jews. The story of Moses reflects the ancient custom of exposure. Hell was thought to be a place where children were burned. The New Testament word for hell is Gehenna, which comes from Ge-Hinnom. Hinnom is a valley near Jerusalem where children were regularly destroyed by pushing them into fire. Infanticide occurred during the eras of Solomon, Ahaz, and Manasseh according to the Bible.

The religious writings of the Hebrews, Mohammedans, and Christians were against infanticide. Until fourth century A.D., however, neither law nor public opinion found infanticide wrong in either Greece or Rome. Constantine the Great, the first Christian emperor of Rome, made two decrees. The first was in 315 A.D. for Italy and the second in 322 for Africa. The purpose was to aid in the maintenance and education of the poor children. The hope was that this would help prevent the exposure, sale, and murder of newborns by parents too poor to rear their children. Not until 374 A.D. did Roman law consider killing an infant murder.

The change in moral outlook towards infanticide was influenced in part by the work of the Catholic Church. This was due to the Church's interpretation of the sixth commandment and from theological doctrine of the soul. People of the time argued that the soul of a child killed shortly after birth could not be punished because there had been no chance for the child to sin. Christian theology countered by using the argument of original sin. They stated that a child is born into sin which can only be removed by baptism. St. Augustine was the main leader and proponent of the theory. He was deeply concerned with the problem of infanticide. He stated in 418 A.D. that the real sin in slaying a newborn was in the deprivation of the opportunity for salvation.[3] Such teachings did have an effect upon infanticide. It is naive, however, to assume that the growth of Christianity automatically made things better for children. At the same time the Church was fighting infanticide, it was also adhering to doctrines seemingly unrelated to infanticide but which affected child murder none the less. Sexual union resulting in pregnancy but not marriage was severely punished. Also the Church maintained a large, unmarried clergy. The above resulted in concealed pregnancy and infanticide. Therefore, while the Church tried to stamp out "legal" infanticide, it made possible many unmarried mothers who were forced to conceal pregnancy to kill illegitimate offspring. This could be said to be the beginning of "illegitimate infanticide" in the western culture.

Early European History Until the 1900s

The Christian preoccupation with original sin created another problem in the form of abandoned children. Since it was now a sin to kill infants people did not want, children were merely left in streets and on doorsteps to either die or be rescued by a sympathetic passerby. In Germany women placed children in front of city council houses. It reached such proportions that a decree by the city council in Basil threatened that in the future any woman caught abandoning an infant would be thrown into the Rhine. The result was an increase in infanticide. In 787 A.D. Datee of Milan founded the first asylum solely for abandoned children.[1] In Russia illegitimate children were called "shameful" children. The earliest provision for such children in Russia dates to 1706 when Novgorod Metropolitan converted the Kolmov monastery into an "orphan-nourisher", imitating the work of Bishop Datheus in Milan. Peter the Great decreed similar orphan-nourishers in 1712-20. He provided windows for secrecy through which mothers could deposit babies. The windows were copied from Pope Innocent III in Rome, who did similar things in 1198. Even though many foundling homes were opened in many countries, they were quickly filled and by 1890 dead babies were still a common sight in London streets. Foundling homes are of importance in the history of infanticide because, although ideally they were supposed to save lives, most infants died due to overcrowding and insufficient number of wet nurses.

Although parents were not now killing these children, society indirectly was.

Continued Evidence of Infanticide

Most evidence of continued infanticide during the middle ages comes from the ecclesiastic section whose purpose it was to prevent the practice. In Rome of 1527 one priest said, ''The latrines resound with the cries of children who have been plunged into them.''[1] By the 1700s there was a high rate of infanticide in every country in Europe. In England, a group of papers called the Essex Records (1570) disclose thirty unwanted babies who were killed. Outright infanticide was less common, however, than introduction of practices designed to be non-life saving, ie. starvation. Refusal to nurse may have been the most common form of infanticide during this period. A high rate of infanticide continued into the 19th century. An 1890 edition of the Encyclopaedia Britannica tells of no signs of lessening of infanticide in Europe. In England in 1871 a select committee from the House of Commons formed to inquire as to the best means of preventing the destruction of infants. They estimated that 80% of illegitimate children died in England during the 1800s because of nurses who would collect fees for accepting responsibility for children, then kill them. Louis Adamic describes a village of such ''killing nurses''. A Russian physician's records from 1855-64 show 343 cases of infanticide, accounting for one fourth of all violent deaths in the area. These only included the cases processed through the courts.

Early Legislation

The problem of infanticide led to the creation and reiteration of laws throughout history in an attempt to halt the occurrence. During the ninth century we find the first specific prohibition against taking an infant into the maternal bed to prevent ''overlaying''. Many of the anti-infanticide laws led to the concealment of pregnancy as stated earlier. Much of the early legislation attempted to deal with the difficulty of concealment of birth then killing the child. Emperor Charles V published a code in 1532 which made concealment of pregnancy and infanticide equally punishable by death. An English Statute of 1623 called it a crime punishable by death to conceal or attempt to conceal birth of a child by secret disposition of its body. English Parliament reduced infanticide from murder to a felony in 1921. Such laws created the problem of determining whether a child was dead at birth or killed later. The medical literature contains numerous articles on methods for a physician to determine such an important fact. When Infanticide was finally considered a crime it was punished severely. As noted before, this really had small impact upon infanticide incidence because people merely became trickier or resorted to less aggressive methods, ie. abandonment or starvation. Not until the 1740s do we find official interest in the causes of infanticide. Frederick the Great noted that the indefiniteness of law, the cruelty of punishment, and arbitrariness of judges were problems in the effectiveness of stopping infanticide. He felt the local authorities should provide for the mother and child, who should remain together.

Infanticide in Literature

There are numerous references to infanticide in the literature from ancient Greece to the present. In Athens the testimony of comic poets frequently allude to exposure of infants. Menander's ''Girl from Samos'' made much fun of a man trying to chop up and roast a baby. The theme of exposure loomed large in myth and tragedy. Shakespeare shows awareness of infanticidal impulses of the mother in Macbeth. Beccaria of Italy felt the murder of illegitimate children was the effect of a cruel social dilemma. Such people led to a period called Storm and Stress in Germany, where writers turned to the causes of unmarried mothers and children. The unmarried mother committing infanticide was the most common literary theme of this period (1770-1800). Goeth in Faust is an example. Infanticide and its prevention was a favorite subject for criminologists of this period also, showing a preoccupation with what was called the most common crime in Western Europe. Great interest was reflected in the number of entrants in a contest in Whitsuntide in 1781. A prize of 100 ducats was offered for the best essay on ''What are the best and most practicable means to eradicate infanticide without promoting prostitution?''

A popular ballad in England, ''The Cruel Mother'', shows a relationship between illegitimacy and infanticide. Writings of Jonathan Swift and Charles Dickens describe the social conditions of children. Tolstoy's play, ''The Power of Darkness,'' revolved around the murder of a newborn child and was based upon an 1880 trial of a peasant. Anton Chekhov, another Russian author, tells of a thirteen year old girl who kills a child in her care by strangulation in his story, ''Sleepy''. When children play London Bridge is Falling Down they are in actuality acting out an ancient sacrifice to a river goddess when the child is ''caught'' at the end of the game. There are many examples of fairy tales in which children are either killed or threatened with death. Such examples include Snow White, Hansel and Gretel, and Baba Yaga — a Slavic tale where children are put into ovens and eaten. Witches in fairy tales reflect real witches in history. Some feel that the witches were old women who were symbols of grandmothers whose death wishes were warded off. Also, old women would typically receive children for a fee, then kill them, ie. the killing nurses mentioned earlier. It is interesting that the punishment for witches and child killers was the same in Salem. The German word hex originally applied to child devouring demons and not human beings. Literature gives us clues to social practices and conditions not present in formal history text.

Theories of Infanticide

Many reasons have been advanced to try to explain why infanticide occurs. A list of such reasons is given in the Table. Most likely all of the reasons and others have contributed to infanticide at some point in time. Awareness of the problem of infanticide has come about through better methods of detection, more acceptable forms of population control, and religious influences. One of the turning points in history came from a realization of the importance of children as potential resources. This came about to a great extent due to the industrial revolution, where children were now valued as workers who brought additional income to the family.

TABLE

Reasons for Infanticide

Societal Stresses and Values
- A. Population control
- B. Illegitimacy in a non-tolerant society
- C. Inability to care for infants: famines
- D. Superstition: Martin Luther ordering mentally defective children drowned as they were instruments of the devil
- E. Ritual Sacrifice
- F. Removal of unproductive members: killing deformed children
- G. Balance the sexes where occupational hazards are high for males
- H. Favoring boys over girls
- I. Greed: killing of children by nurses for money
- J. Power: Herod slaying babies to eliminate a possible rival

Family Stresses and Values
- A. Inability to care for infants: first of twins, close spacing
- B. Superstition
- C. Population control
- D. Post partum depression
- E. Protection of mother: A fear of the husband's faithlessness while the mother is nursing in societies where intercourse is forbidden during this period

Trends through History

Although boys tend to have a lower survival rate in nature, throughout history girls have been more likely to be killed. In most cultures boys were desired over girls for a variety of reasons, including expense of providing a dowry for the girl, and better assurance for the parents in old age because the son could support them. Jack Lindsay stated, “Two sons are not uncommon, three occur now and then, but more than one daughter is practically never reared.”[1] There was an old belief in parts of Europe that milk from mothers who delivered girls was best for newborn boys. This led to abandonment of girls by mothers who sought employment as nurses. Such factors contributed to a surplus of boys over girls in most of Europe between 1450-1750. Infanticide of boys and girls approached equality for illegitimate babies, however, as the child was not wanted.

There have been some interesting trends throughout history. In prerecorded history we find infanticide to be culturally accepted and in some cases enforced by law. With the intervention of the Christian Church, infanticide changed. This was the beginning of illegitimate infanticide. A little later on there is another milestone. Writers and some political leaders in Europe became concerned with infanticide as the result of a great social dilemma. During the late 1800s and early 20th century infanticide is considered murder but it is still separated in people's minds from murder of adults. There is a value judgment that killing babies not old enought to experience fear is different from murder of adults. As late as 1911 Dr. Mercer, an English physician, stated, “In comparison with other cases of murder, a minimum of harm is done by it . . . The victim's mind is not sufficiently developed to enable it to suffer from the contemplation of approaching suffering or death.”[3] Now today we find infanticide, at last, included in the much broader category of child abuse. Infanticide still occurs today in most of the world. There are still problems of concealment of pregnancy and birth then murder of the infant. There is still death culminating from the final stage of child abuse.

Summary

Even considering the probable inaccuracies of figures and statistics reflecting the amount of infanticide in early history, it is evident that infanticide has occurred since earliest time. Infanticide can be documented for most cultures at some point in history. Infanticide, ". . . has from time immemorial been the accepted procedure for disposing not only of deformed or sickly infants, but of all such newborns who might strain the resources of the individual family or the larger community."[5] Perhaps a better understanding of the history of infanticide will enable us to more effectively prevent both infanticide and child abuse.

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Special Article

Preschool Screening: Right or Ritual?

JOHN F. HICK, M.D.*

The Minnesota Preschool Screening Program attempts to accomplish comprehensive health and educational screening for four to five year old children on a voluntary basis through state funding. The background, components, and operational aspects of the program are reviewed.

> "The legislature finds that early detection of children's health and developmental problems can reduce their later need for costly care, minimize their physical and educational handicaps, and aid in their rehabilitation. The purpose of this act is to assist parents and communities in improving the health of Minnesota children and in planning educational and health programs."
>
> — Minnesota Preschool Screening Act, 1977

THE "KINDERGARTEN CHECKUP" is an American institution that has changed little throughout the years. The Minnesota Preschool Screening Program (PSS) represents a significant departure from this tradition. With emphasis on comprehensive screening for health and developmental problems, maximal reliance is placed on volunteers and nurses to accomplish the screening. Physicians could exchange the role of screener for that of screening consultant. Primary care pediatricians and family practitioners in the state need to be aware of the full implications of this act in order to assess the validity of the legislature's thesis in funding the program and to oversee appropriate implementation of the program through local school boards.

Four influences have been important in the evolution of Minnesota PSS: (1) a federal mandate to identify preschool children at risk for educational failure, (2) a trend toward increased involvement in health maintenance within the nursing profession, (3) the existence in Sweden of a successful and almost identical screening program for four-year-old children during the past 10 years and (4) an effort at the state level to promote the Early and Periodic Screening Program (E.P.S.). State regulations specify that school districts must contract with E.P.S. programs to conduct preschool screening if such programs are locally available.

The Education For All The Handicapped Act, passed in 1975, obligates all states to identify and provide services for every preschool child who has a potential educational handicap. Failure of any state to implement programs for identifying eligible children before kindergarten entry in 1978, and beyond, would mean forfeiting federal special education funds. Minnesota state law presently provides special education services for children who are 4 years old or older who have mental deficiency, specific learning disabilities, emotional disability, speech defect, deafness, and blindness. Accordingly, preschool screening optimally should be performed one year before entry into kindergarten.

As originally conceived, Minnesota PSS was intended to enable nurses to perform all screening procedures at one site. Long an underutilized force in the health manpower scheme, school nurses are in a transitional phase, illustrated by the School Nurse Practitioner movement. Conceived by Henry Silver, the University of Colorado pediatrician who originated the Child Health Associate Program in the 1960s, School Nurse Practitioners are trained to assume the following responsibilities: (1) health screening, (2) nutritional counseling, (3) health education, (4) health assessment of children with learning problems, and (5) identification and counseling for the emotional problems of school-aged children.[1] A Robert Wood Johnson Foundation grant supports five prototype School Nurse Practitioner training programs presently active in the country. The University of Colorado program involves 4 months of didactic work and 8 months of supervised field work. These programs have sparked considerable controversy concerning the optimal setting for providing health maintenance to school-age children. A fundamental question in Minnesota PSS is whether school nurses with Minnesota Department of Health (MDH) training alone, rather than the more extensive experience in a Nurse Practitioner program, are fully qualified to undertake health screening.

Since 1969, expansion and standardization of preschool screening for four-year-old children in

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Sweden has, coupled with an aggressive outreach effort, improved the compliance with voluntary screening for this age group from 56 to 96%. Two important factors, however, mitigate against applying such a program to Minnesota with the same high degree of success. First, because health care is nationalized in Sweden, implementation of any mass program is simplified, in contrast to the dual existence of health maintenance programs in both the public and private sectors in Minnesota. Second, outreach is greatly enhanced in a country such as Sweden, where a National Registry of Citizens permits rapid, computerized identification of all children eligible for screening at a given age. The Wagner report of the Swedish program[2] serves as the basis for references to the Swedish experience contained in this review, unless otherwise specified.

The merits of the individual program components in Minnesota PSS will be reviewed with reference to some of the largest published studies available, with emphasis on the more controversial components.

Details of the Minnesota program can be obtained by writing to the Pupil Personnel Services Division of the State Department of Education, for a copy of the administrative manual. Complete referral criteria for the health components will be found separately in the administrative manual for E.P.S. Participation in the program is voluntary and parents may register a child for any elected screening component to the exclusion of others. History or physical examination performed by a physician in the previous year will not be repeated.

Specific Preschool Screening Components

Health Questionnaire

Predicted Yield — Nearly all the major physical handicaps that might have a potential impact on educational planning should be identifiable through use of the questionnaire.

A health questionnaire has been substituted for a routine prekindergarten physical examination in the Rochester, Minnesota, Public School System during the past five years. Previous experience had shown that the average five-year-old child followed from birth had been examined on 14 separate occasions. In a retrospective study of 382 such children, Colligan and O'Connell noted that the prekindergarten examination revealed no new significant physical defects other than those related to vision or hearing.[3] A prospective formal study to detect the number of children with significant health problems not identified by the questionnaire has yet to be undertaken, but health personnel involved believe that very few major health problems have been missed. Clearly, this experience may not parallel that of communities whose resources for health maintenance in early childhood may be inadequate.

Completion of a health questionnaire should be mandatory to school entry as a data base for use by authorized school personnel.

In addition to identifying previously recognized health problems, the health questionnaire used in Minnesota PSS is also designed to identify children with significant unrecognized health, developmental, or psychosocial problems through a review of symptoms. In Sweden, 3% of four-year-old children who are screened are referred for behavioral problems. More importantly, screening has reportedly increased parental awareness of mental health development and acceptance of counseling about such issues as offered through child health centers where screening is performed.

Immunization Status

Predicted Yield — According to a 1977 MDH survey, 29% of kindergarten children in Minnesota have had three or fewer DPT immunizations and 21% have had fewer than three oral polio doses.

State-mandated completion of DPT and oral polio immunizations to complement required measles and rubella immunizations went into effect in 1978. State action is part of a federal effort to achieve optimal immunization levels in the child population.

Vision and Hearing Screening

Predicted Yield — Since its inception in 1959, the Minnesota Medical Association-sponsored screening program has shown that 6% of children have defects of vision and 9% have hearing defects.

Identification of reversible defects of vision and hearing is critical to the educational goals of any preschool screening program and will undoubtedly remain the keystone for such programs. Detection of strabismus in this context has been particularly important in order to prevent amblyopia.

Dental Screening

Predicted Yield — Routine dental screening reveals that approximately half of all four-year-old children have caries.[4] The emphasis in Minnesota PSS is on referral and on dental health education. The Minnesota Dental Association is concerned that dental screening conducted by a nurse may lead to a significant number of false-negative results and has persuaded the health department to adopt a policy that all children who have not been examined during the previous year by a dentist should be referred. On one level, this displaces any value that the oral inspection might have, but compliance with the recommended referral might be enhanced through identification of an actual defect which the parents had not previously recognized. Conversely, a negative screening exam might dissuade parents of the need for an annual dental exam. Dental screening for the Medicaid-eligible population served through the E.P.S. program is especially relevant because treatment benefits are available through the program. In Sweden, dental screening has been shifted from age 4 to age 2 in order to introduce preventive dentistry at a more optimal age.

Developmental Screening

Predicted Yield — Seven percent of children ages one month to six years have been found to have an abnormal or questionable Denver Developmental Screening Test, meriting more intensive psychoeducational evaluation.[5] A 0.6% incidence of preschool developmental language disabilities can be expected.[6]

In line with the federal mandate to identify educationally at-risk children at an early age, developmental screening is one of the more promising aspects of Minnesota PSS. Many school districts have offered readiness screening before entry into kindergarten, but screening for developmental problems as early as 1 year before school entry on a uniform systematic statewide basis has never been undertaken.

Formal IQ testing at four years of age will show a significant correlation with testing at later ages.[7] However, for five-year-old children, there may be better predictors of school failure than IQ testing. For example, a parent's description of the child's use of language at home and letter matching exercises have high predictive value.[3] Thus, it may be a positive form of compromise that Minnesota PSS standards have been relaxed to permit use of locally developed general screening instruments, for which local norms have been established, rather than insisting on the use of standardized screening tests.

No consensus has been reached as to the simplest, most reliable standardized screening tests. The Denver Developmental Screening Test is the most widely used early childhood developmental screening test. It is applicable at least until four and a half years of age, and offers a comprehensive developmental profile though it may not adequately test for speech defects. The test yields a false-positive rate of 11% and a false-negative rate of 3%. The predictive value of the DDST for school performance has been evaluated, but not extensively. While 88% of children with an abnormal DDST during the preschool years showed, on follow-up to third grade, evidence of a significant learning problem, 32% of children with a normal preschool DDST showed later evidence of learning problems.[8]

The study was undertaken in a lower socioeconomic population and testifies to the overriding influence of environmental factors, in contrast to developmental potential, as determinants of a successful educational experience. More studies of the predictive value of the DDST and of other preschool developmental screening instruments are needed.

The DDST will reliably identify children with mental retardation and those with severe emotional deprivation, and some children with markers for potential learning disability such as speech defect, incoordination, and hyperactivity. There is no uniformly reliable means for identifying the child with a potential for specific reading disability at 4 years of age. A more appropriate time to screen for a potential reading disability probably is during kindergarten.

There are several advantages to early identification of developmental problems. Appropriate counseling and educational planning for children with mental deficiency can be undertaken. For the child with borderline learning potential, early identification may: (1) encourage home stimulation programs for deprived children, (2) avoid enrollment in kindergarten on the basis of chronologic age alone, and (3) permit mainstreaming at the time of school entry and after remedial services have been introduced (avoiding the more costly alternatives of special education or self-contained classrooms). However, it remains to be seen whether early intervention will result in augmented or decreased long term educational costs.

Screening for speech defects and for language disabilities such as developmental aphasia in the preschool years is important, because this is the most critical age for language development and an optimal time for intervention, even though most of the problems identified may be self-correcting speech dysfluencies. Unfortunately, there is no consensus as to the best approach to screening preschool children for speech problems, largely because they are often inhibited enough in a strange environment that adequate sampling of speech is almost impossible.[9]

Physical Measurements

Height-Weight — Predicted Yield — 3% incidence of short stature and 15% incidence of obesity.

Generally, organic causes of short stature that are apparent at the age of four years will have been identified at an earlier age. In most of the remaining instances, the causes will be of a nontreatable genetic or constitutional nature.

Identification of obesity at an early age can be potentially beneficial if appropriate follow-up resources are available; otherwise the screening is pointless. Observation for obesity is more reliable for diagnostic purposes than is the use of a weight or height table. If such tables are used, according to the Ten State Nutrition Survey (TSNS), a weight that is 110% of normal for height and sex is a more appropriate cutoff point for obesity in the preschool age child than 120%, the value conventionally applied to adult screening. The 110% corresponds roughly to 1 SD above the mean value for the triceps fat folds.[10] Five percent of 4-year-old children can be expected to be very obese.

Obviously, interpretation of borderline measurements will be impossible without reference to either previous or subsequent measurements. Distinguishing undernutrition from constitutional factors according to single sets of measurements is virtually impossible.

Blood Pressure

Predicted Yield — The incidence of hypertension in school children is 0.3%.

A sustained blood pressure above the 95th percentile in the preadolescent age group (six to 12 years) is rare, according to the Muscatine study.[11] Fifty percent of the hypertensive children in that study were obese, 25% had essential hypertension, and 25% had secondary causes of hypertension.

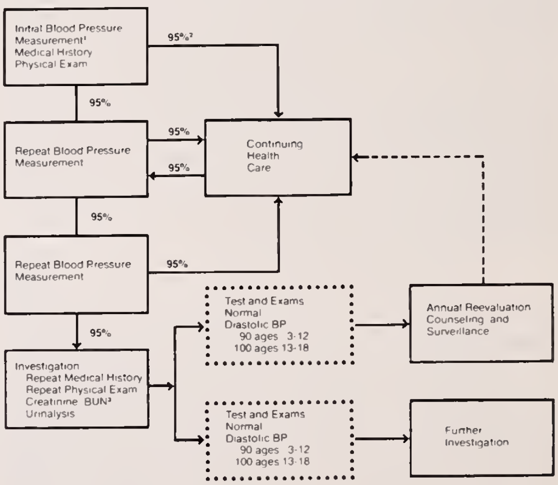
Mass screening for hypertension in childhood is defensible only for identifying secondary hypertension, because just one child in 1,000 in the Muscatine survey of preadolescents was found to have essential hypertension. If early salt restriction and weight control will modify the natural history of essential hypertension during the developmental years, most of the at-risk children will not be identified through use of available diagnostic criteria.

The Muscatine study concluded that mass screening for hypertension was not cost-effective, but for clinical purposes, in contrast to research, the laboratory tests obtained in this study were probably excessive. The Task Force of the Heart, Lung, and Blood Institute on control of blood pressure advocates mass screening only if rigid provision for education, referral and follow-up are ensured. The Task Force recommendations regarding follow-up are reasonable and should be adopted (Figure).[12] Obviously, no child who does not have sustained hypertension should be labeled as being hypertensive. The most important aspect of follow-up is that more intensive laboratory evaluation than urinalysis and serum creatinine determination would not be indicated unless warranted by history, by physical examination, or by a sustained diastolic pressure higher than 90 mm Hg. In the Muscatine study, all children with secondary hypertension were diagnosed on the basis of history or physical examination. None of the 3,000 children screened in the six to 12-year-old age group had a sustained diastolic blood pressure of more than 90 mm Hg.

Screening Physical Examination

Predicted Yield — Less than 1% incidence of new significant physical handicaps.

The nurse-conducted physical examination is the most controversial feature of the preschool screening program. It amounts to a routine physical examination evaluated on a qualitative basis, the individual components being judged normal or abnormal, with the emphasis on referral of the abnormal rather than on diagnosis. To be eligible to conduct such an examination, nurses must take a three-day course sponsored by the Minnesota Department of Health (MDH). This didactic course is well conceived and emphasizes potential findings appropriate for the referral of the preschool age child. However, practical experience in examination is limited, provision being made for examination of only a few children. Aware of this deficiency, the interagency committee for the state departments of education and health accepted the following additional recommendations of an ad hoc committee: (1) a Pediatric Nurse Associate (PNA) or physician must be in attendance in a supervisory



Blood pressure measurements should be made at 1 4 week intervals

[1] If initial blood pressure measurement taken at school or other community center two subsequent blood pressure measurements should be made prior to referral of patient if feasible

[2] The 95 percentile is an arbitrary statistical cutoff point children with blood pressure at the 95 percentile should be labeled as having high normal pressure rather than being hypertensive

[3] Optional If patient is obese or a cause identified for hypertension BUN or creatinine may not be indicated

Figure — Heart, Lung and Blood Institute Algorithm for blood pressure screening. (By permission.)

capacity for the initial mass screening examination if screening physical examinations are performed by a registered nurse with the minimal required training, (2) a validation study of the nurse examination is to be conducted, and (3) an on-going recertification process is to be devised for nurses conducting the examination. These provisions contribute to but do not assure quality control. The validation study, for example, will not be conducted for 3 years, permitting three years of uncontrolled experimentation.

From a legal point of view, the Nurse Practice Act of Minnesota permits nurses to conduct screening physical examinations. However, nurses so involved are subject to malpractice claims and should be protected with malpractice insurance.

In general terms, the value of anyone, however qualified, conducting a routine examination of four to five year old children can be disputed if regular examinations have been performed through the first year of life. On such children, only 1% of examinations at one year of age yield significant new abnormalities.[13] The previously cited Rochester, Minnesota, experience with preschool children is substantiated by a Swedish study of 2,500 four-year-old children whose last previous examination was at one to two years of age. In the author's words, "Practically all serious handicaps were detected and already taken care of before the age of four years."[14]

Physical problems that could not be detected through any other phase of the preschool screening process and that might not have been detected in infancy would include occasional congenital heart disease (0.1% yield in Sweden), undescended testis, and inguinal hernia. Otitis media is the most frequent physical problem found in surveys of this age group in some studies, but four years of age is a peak age in the natural history of serous otitis media and acute otitis media.[4] In the asymptomatic four-year-old child with normal hearing, long-term benefits of screening otoscopy are unproved. All other potential physical problems in the four-year-old child are so infrequent or inconsequential as not to merit comment.

Because of the documented low yield from physical examinations at the age of four years, there is a strong argument for omitting the controversial screening examination and simply referring a child for physical assessment by an appropriately licensed professional if an examination has not been performed during the previous two to three years. This would then be analagous to the state policy regarding referral for dental assessment.

Nutritional Evaluation

Predicted Yield — Malnutrition will be rare but unorthodox eating habits common.

The nutritional evaluation is to be conducted through use of a 24-hour diet diary of the child's "typical" day. This is only an approximate reflection of the child's true diet pattern and cannot reliably be interpreted in quantitative terms.

Programs for undernutrition should be directed at the appropriate target population. The TSNS showed a correlation between undernutrition and socioeconomic status. Availability of nutritional counseling to disadvantaged populations in well-child clinics, providing a point of entry to food supplementation and social programs, offers the best hope for preventing undernutrition. After-the-fact screening is a lower priority matter for which reliable diagnostic criteria that can be simply employed are not available.

The quality of the diet according to the TSNS showed no relationship to economic status, and thus, nutritional screening for omission of major food groups and for excess snacking may be appropriate in the general population. Minnesota PSS will concentrate on detecting omission of two or more major food groups. The true extent of snacking, however, likely will be underestimated by the 24-hour diary.

Unfortunately, there is no easy means of measuring the outcome of a nutritional screening program. It is possible that nutrition education would be more effective than mass nutrition screening and more cost effective, especially if coupled with dental health education.

As with all other aspects of screening, there is no purpose in nutritional screening if appropriate follow-up services are not available. Where such services are available, a detailed nutritional evaluation should be undertaken for all children with nutritional anemia, physical evidence of undernutrition, obesity, or multiple dental caries.

Laboratory Evaluation:

Test	**Predicted Yield**
Hemoglobin	5% incidence of iron-deficiency anemia.
Urinalysis	1 to 2% incidence of albuminuria and a 0.5% incidence of hematuria.

The preschool age does not represent a growth spurt phase and thus is not a critical age for detecting iron-deficiency anemia; less than 1% of this group will have a hemoglobin level below 9.5 gm%. However, correcting for social class, 15% will have evidence of iron-deficiency as reflected in transferin-saturation levels.[15] The health consequences of very mild iron-deficiency anemia are not well documented. Generally, the treatment of iron-deficient two-year-old children (average hemoglobin level of 8.7 gm%) will cause a significant increase in IQ scores, compared with the IQ scores of a nontreated control group, between five and eight days after iron supplementation is started.[16] A similar response probably would not be demonstrated in four-year-old children — a group that tends to have milder iron deficiency.

Other causes for anemia detected on a screening basis will be rare and generally are nontreatable. The state program provides screening for sickle cell anemia in the susceptible population, although the most critical age for detection of this disease is during infancy.

Follow-up evaluation of anemia detected through screening dictates confirmation of evidence of iron deficiency by means of a peripheral smear, transferin saturation evaluation, or red cell indices before iron therapy is begun and before further diagnostic evaluation is considered.

According to the E.P.S. guidelines, reproducible albuminuria of grade 1 (30 mg/dl) is a criterion for medical referral. Kunin has shown that 10% of children will have this degree of albuminuria but that fewer than 20% of the specimens also will be positive for protein using the heat and acetic acid method. If grade 2 (100 mg/dl) albuminuria is used as the cutoff level, 1 to 2% of grade-school children will have proteinuria. For 95% of these, a first voided morning urine specimen will be protein free, thus suggesting the comparatively benign orthostatic pattern.[17] When a very strict criterion was used for proteinuria (100 mg/dl on at least two occasions), only 0.5% of 2,300 grade-school children in a Canadian study were considered to have proteinuria.[18] Although an abnormal cause for isolated proteinuria rarely will be found, 9% of the children with proteinuria in that study had radiographic evidence of pyelonephritis.

Testing for proteinuria is no longer routinely done on 4-year-old children in Sweden because of the resulting low yield of identifiable pathology.

Urinary infection is the only common treatable condition that might cause proteinuria.

The more sensitive test for urine infection, the urine culture, has been deleted from the Minnesota PSS regulations. Even so, screening for asymptomatic bacteriuria may still be performed on an optional basis. If radiographic evaluation of school-age children with asymptomatic bacteriuria is negative, the outlook without treatment appears to be good, but long-term radiographic follow-up beyond the limits of the present studies (two to three years) is necessary before reliable conclusions can be drawn. Vesicoureteral reflux or parenchymal reduction (usually both) will be found in 10 to 20% of preschool-age girls with asymptomatic bacteriuria.[19] If untreated, a small but significant proportion of these children will have evidence of progressive radiographic deterioration.[20]

The Section on Urology of the American Academy of Pediatrics recommends that screening of preschool children for asymptomatic bacteriuria should be continued and the results evaluated. Ideally, such screening should be conducted in medical centers prepared to evaluate outcome in a systematic fashion.

Rarely will a treatable cause for microscopic hematuria be found through routine urine screening. It is not a reliable screen for Wilms' tumor, even if performed frequently, because only 25% of children with Wilms' tumor will have hematuria at the time of diagnosis. In the Canadian survey of grade-school children with microscopic hematuria, only one in 36 had abnormalities on intravenous pyelograms. Most of the children presumably had either benign recurrent hematuria or nontreatable nephritis.

Discussion

The Minnesota preschool screening program is an ambitious attempt to accomplish a comprehensive health and developmental profile on all 4-year-old children. It remains to be shown whether enough important, treatable, previously unrecognized problems will be identified through the expanded preschool screening process to justify the effort. Screening is very useful for major health problems amenable to treatment at a critical point in time, for example, congenital hypothyroidism, strabismus, and scoliosis. Multiphasic screening for either insignificant or nontreatable problems cannot be justified in a cost-benefit analysis. Minnesota PSS bridges this screening spectrum. Cost-benefit analysis is important not only in assessing the relevance of individual screening components but also in determining through legislative review what overall direction the program will take. A comprehensive screening program should logically be blended, insofar as possible, with the existing health care delivery system. A more selective preschool screening program could be carried out exclusively by nurses and volunteers in a nonmedical setting.

Minnesota PSS is an experiment, the preliminary results of which are under review by the state legislature. Several factors in addition to the cost-benefit ratio must be considered in assessing the impact of the program. Logistic issues are especially important. The most frequent complaint of physicians about Minnesota PSS is that it represents a fragmentation of medical care. The establishment of one-time screening clinics in communities well-endowed with services to provide for continuity of care can be counterproductive. The Minnesota Medical Association has successfully secured the eligibility of private physicians as screening providers, either within the customary office setting or at a separate screening site.

The two-hour duration of the screening process may be a deterent to participation in the program by some parents and therefore may detract from the outreach effort for the more critical screening components, such as vision and hearing. In Sweden, screening is divided into two visits. Although two-site screening programs may enhance the validity of the screening process (e.g. nurse vs. physician or PNA physical examination), they are less desirable administratively than is single-site screening.

The responsibility for screening the preschool child should not be a contest between physicians and school nurses. A mutually agreeable working relationship needs to be established. Schools may be the ideal setting for providing health maintenance to school-age children. For example, the establishment of nutritional counseling in the schools where ease of access to the child; the opportunity to monitor height, weight, and blood pressure regularly; and the availability of supervised fitness activities combine to create an optimal setting for managing obesity. Such a program has been successful in a limited pilot study of obese fourth grade children in the Rochester, Minnesota, Public Schools.[21]

Availability of treatment resources affects the selection of screening components. Screening for relatively rare but important problems, such as strabismus, must be carried out irrespective of local availability of services, while screening for more common problems, such as dental problems and obesity, is pointless unless adequate services are available locally or unless the screening prompts development of such services.

Ultimately, follow-up is the most critical phase of the screening process. Outcome analysis of Minnesota PSS will be conducted jointly by the state departments of health and education and will basically include an inventory of the problems identified and an analysis of compliance with follow-up. Tentative plans exist to randomly sample parents by questionnaire for their response to the program. Data on verification of the problems identified probably will not be available. An analysis of participation according to socioeconomic class needs to be made. If the lower socioeconomic population is poorly represented, the children at greatest risk for health and developmental problems will have been missed. The results of educational or medical intervention will be the most important measure of success of Minnesota PSS, but there are no plans for a systematic evaluation of the experiment at this level.

One of the principal failings of the federal E.P.S.D.T. program is failure to generate sufficient data to permit valid conclusions about the impact of the program. The same potential pitfall can be anticipated for Minnesota PSS. Even in Sweden, the screening of 4-year-old children is judged successful more on the basis of public acceptance than on objective, cost-benefit analysis.

Funding issues may figure prominently in the legislative review. Strong anti-inflationary sentiment could bring radical reduction of the program without regard to program merits. At present, the federal matching funds for special education are meager and require a high state-to-federal matching ratio. Thus, the most unfortunate feature of Minnesota PSS so far is that it has been introduced on a crash basis in order to meet a federal deadline regarding identification of developmental handicaps. New and unproved screening programs should first be introduced on a pilot study basis, limited, for example, to a few representative school districts. Had this approach been taken, money would undoubtedly been saved, the screening program streamlined, and trial and error confusion avoided, despite keeping the federal dollar temporarily in limbo.

Minnesota PSS does represent a sophisticated approach to preschool screening, has renewed interest in the subject, and has forced the professions involved to dust off this old tradition for a comprehensive reappraisal.

Conclusions

1. Minnesota PSS is an ambitious effort to provide comprehensive preschool Screening for health and developmental problems.
2. The movement points out the need to more intensively explore means by which the medical community and schools can collaborate to provide health maintenance activities.
   Schools deserve an opportunity to become acquainted with the health and developmental status of preschool children. Mandatory rather than voluntary completion of a health history questionnaire by parents would facilitate this involvement and provide a data base in the schools for future reference.
3. Most major physical abnormalities will have been identified during routine checkups during the first year of life and routine preschool physical examinations will produce a low yield of significant new problems.
4. Of the newly proposed screening components, developmental evaluation of the preschool children should identify the greatest number of children with previously unrecognized, potential

education problems. This is one of the prime objectives of the federal Education For All The Handicapped Act.

5. The yield from screening probably will be greatest in communities with the fewest diagnostic and therapeutic services. Through the screening process, however, augmentation of such services may come about but perhaps not without state or federal subsidies.
6. The legislative review of Minnesota PSS will result in consideration of at least three alternatives to the original program: first, further absorpition of comprehensive screening into the existing health care delivery system; second, recasting the program as an abridged, selective screening plan, which could be carried out exclusively by volunteers and paraprofessional personnel in a nonmedical setting; or third, discontinuation of the program.

   If it can be shown that correctable deficiencies are being identified with a frequency sufficient for benefits to outweigh the costs of screening and that adequate follow-up is carried out, continued application of specific screening components can be defended. Otherwise, legislative support should be withdrawn.
7. Major cutbacks in the screening process could be a blessing in disguise for the public by permitting more emphasis in the screening setting on health education, for example, dental health and nutritional education. Education potentially benefits everyone; screening, at most, benefits those with previously undetected problems.

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(Continued to Page 382)

(Continued from page 381)

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(Continued to Page 384)

(Continued from Page 383)

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Anderson, C. F. Co. 344

Army Reserve 336

Beltone Electronics Corp. 334

Burroughs-Wellcome Co. 326, 348

Classified Advertising 381

Health Central 310

Lilly, Eli & Co. 312

Mead Johnson Pharmaceutical Division 327

Medical Protective Company 340

Merrell-National, Inc. 328, 329, 330, 344, 345

Merck Sharp Dohme 310

Metro Surgical Supplies, Inc. 336

Minnesota Medical Association 338, 342

Pharmaceutical Manufacturers 366, 367

Roche Laboratories . . . . . Cover 2, 325, Cover 3, 4

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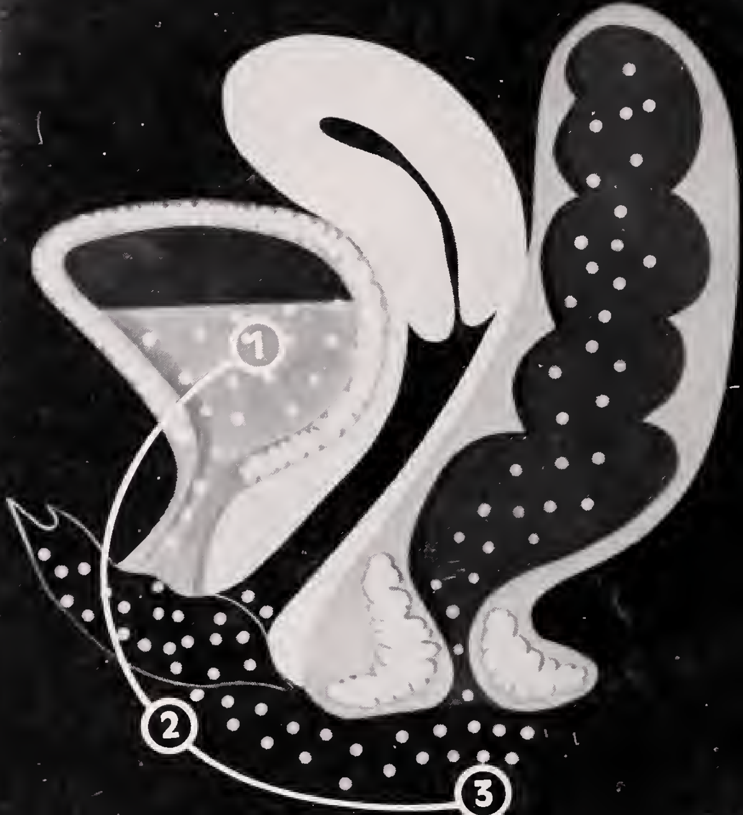

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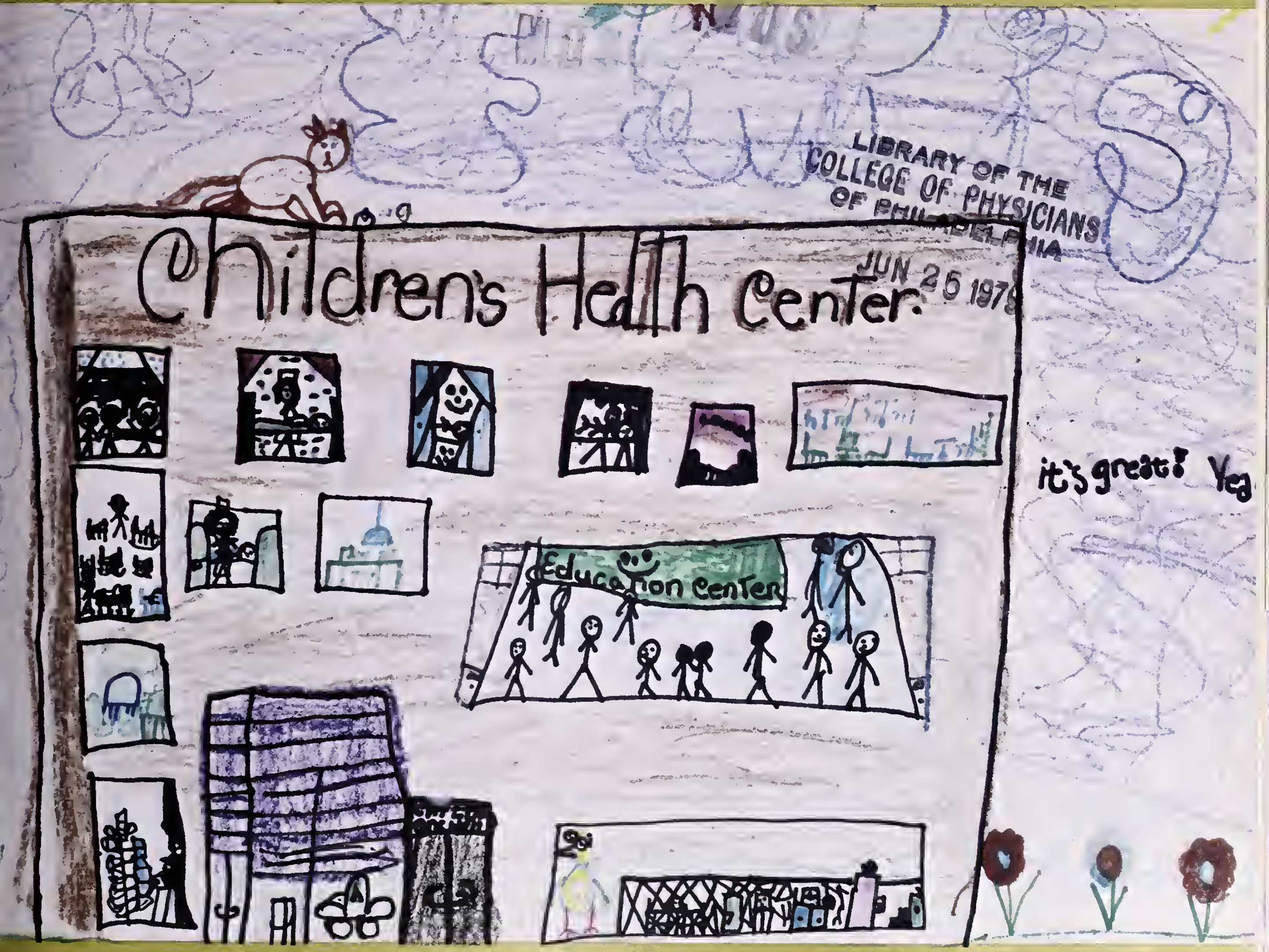
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Contents — June, 1979

COVER DRAWING — "It's A Great Year for Kids, 1979"
Andrea Brown 398

PRESIDENT'S LETTER —
Frank E. Johnson, M.D.
President, Minnesota Medical Association 389

EDITOR'S NOTEBOOK — "... Power, Finances, and Government, and Rather Less about the Humanistic Aspects of Medicine"
Richard L. Reece, M.D.
Editor-in-Chief 391

CANDIDACY —
"Robert T. Kelly, M.D."
Haddon Carryer, M.D.
Alternate and Delegate to AMA 1964-1978 395

EDITORIALS

1979 — Beyond Forgiveness?
David Raoul Brown, M.D., Guest Editor 397

The Fruition of a Dream
Daniel J. Whitlock, M.D. 398

ORIGINAL CONTRIBUTIONS

Anterior Cranial Vault and Bony Orbit in Infancy
Bruce B. Shilling, M.D. et al. 399

Advances in Oral-Facial Deformity Reconstruction
Franklin R. Stickel, D.D.S., M.S.D. et al. 405

Pediatric Cardiology at Children's Health Center — First Five Years
Harold Katkov, M.D. 411

Meconium Aspiration Syndrome — Treatment of the Clinical Problem
David B. Klain, M.D. and G. Eric Knox, M.D. 417

Lateral Decubitus Radiograph of the Chest in Pediatric Radiology An Additional Use
Leland H. Prewitt, Jr., M.D. and Shashikant M. Sane, M.D. 423

The Use of 1-desamino-8-D-arginine Vasopressin (DDAVP) in the Management of Neurogenic Diabetes Insipidus (Multiple Etiologies in Pediatric Patients)
David R. Brown, M.D. and Donald L. Uden, Pharm. D. 427

Febrile Convulsions — Current Controversies
John T. MacDonald, M.D. 433

Uncommon Inguinal and Scrotal Lesions in Infants
Bernard J. Spencer, M.D. 435

Fetal Turner Syndrome
R.M. Drake, M.D. and R. A. Franciosi, M.D. 443

Diagnostic Uses of Anorectal Manometry in Pediatrics
Felix A. McParland, M.D. and Karen Olness, M.D. 447

Idiopathic Thrombocytopenic Purpura in Childhood
Lawrence J. Singher, M.D. 455

RHEUMATOLOGY CORNER — Juvenile Rheumatoid Arthritis
H. D. Venters, M.D. 463

BOOK REVIEW — The Rise of Surgery — Wangensteen and Wangensteen
Carl O. Rice, M.D. Editor Emeritus 390

CLASSIFIED ADVERTISEMENTS 467

INDEX TO ADVERTISERS 470

The drawings published throughout this issue are the creations of the children patients of Children's Health Center in Minneapolis.

Volume 62:6
Pages 385-472

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President's Letter

It seems appropriate for me to reflect briefly on the year just spent as President-elect of the Minnesota Medical Association. It has been an interesting, enjoyable and educational time, during which I have tried to prepare myself for the coming year. Since there is no prescribed course of preparation, I have done my best to get a grasp on how the various organizational parts function and relate to one another. Study of the table of organization is helpful but, in itself, is a lifeless, skeletonized picture of the association. That skeleton, increasingly, takes on form and life, however, as one logs hours of attendance at the many and varied committee meetings. During this period, my previously somewhat vague picture of the association has been made much clearer. In this process of clarification, I could not help but be tremendously inpressed and grateful that so many talented association members give so generously of their time, thought and energy to these necessary committee functions.

As might be expected, I have paid close attention to the behavior of the several past presidents who continue to be active and serve on many important committees. I have learned a lot from these men and am glad that, in our association, old presidents do not fade away but, instead, such men as Chester Anderson, Richard Anonsen, Roy Diessner, Barnard Hall, Robert Kelly, George Martin and John Regan continue to serve in various capacities and to give us the benefit of their accumulated knowledge and wisdom. I understandably paid closest attention to the conduct of my immediate predecessor, Dr. Robert Flom, and to Richard Frey, then Chairman of the Board. I recognized each of them as highly talented persons who have given of those talents unselfishly. Each has provided an example worth emulating. We should be aware that quality persons, such as these, have many demands upon their time and numerous opportunities to serve. The fact that they have chosen to serve MMA is taken to be a high compliment and indicative of the relative stature of our organization.

There is no doubt that physician-member activity is essential to the life, vitality and growth of the association. Such activity deserves credit but without administrative staff to provide continuity and to organize, round out and develop the thoughts, ideas and directives generated in the various committee meetings, our efforts would be completely ineffective. The staff has impressed me from top to bottom as being very hard-working, dedicated and responsive to the association. Without exception, they seem devoted to the cause of medicine and protective of the principles for which we stand. In fact, the staff is often first to recognize a threat to those principles.

As busy and involved as members of the association and staff have been in the past, I believe, that the future will demand even more. Our society is now in the process of molding the medical care system of the future for America. We have an obligation as the most knowledgeable members of society to inform the lay public and health planners of what we believe to be the *essentials* of good medical care and what such care should cost. It seems only fair that the citizenry be as fully aware and as completely informed as possible when it makes the day to day decisions which will shape the form of our medical care system. We must continue to expand our educational effort, therefore, not as a physicians' special interest group but, rather as citizens concerned for the general welfare, strength and health of our nation. Such an effort will require more money, more staff time but, most important, the time and talent of more physicians.

To meet the needs of the future, I will search for ways to generate income for the association which would serve to spare the dues dollar. I am also deeply interested in recruitment of vital new members, particularly from among the younger physicians coming into practice. I would enlist the aid of each of you in working toward these objectives.

As the mantle of the presidency settled about my shoulders, last month, I felt a warm and comfortable sensation. The warmth comes from the fact that my peers hold me in sufficient regard to trust the office to me. The mantle rests comfortably because I know that I am not alone, but will have the help and guidance of the many talented persons who make up our association. This, being the case, I cannot help but be optimistic that we will continue to grow in purity, wisdom, strength and influence as we strive to achieve for society the essentials of ideal patient care.

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

Book Review

The Rise of Surgery — Wangensteen and Wangensteen.
University of Minnesota Press. 39.50

"The Rise of Surgery" by Wangensteen and Wangensteen is an excellent example of detailed research in medical history, compiled in 26 delineating chapters. It is the acme of surgical history from the beginning of recorded time, and for the historical novelist of the future, this book would serve invaluably in providing accurate reference for items of personality concern: "The unjust obliquy to the word 'nurse' ", (page 344); "The Abuse of the Parish Beadle" (page 340); "The philosophic dissertations of early surgeons," called "The filling of your belly with east wind,", (page 13), and numerous other valuable references.

In a few instances the authors referred to related historical events out of sequence, leaving the reader with the responsibility of sorting them out.

The chapters dealing with war surgery were well written and fascinating. Many are the advantages that accrue to the progress of medical science during periods of stress, such as is to be expected in war time: irrigation of the wound with water by Trielliere, 1808; the value of nurses in the care of patients by Wells, 1855; early antiseptics were largely prostate from bromide to nitric acid, 1863, phenol 1870, chlorine 1917, sulfa 1935, and penicillin 1939.

I can most heartily recommend this volume to all readers and particularly to surgeons who are interested in the fascinating events of history. The authors are to be commended for their diligence, their devotion to detail, and their ability to compile this history. Dr. Wangensteen's numerous former students and colleagues will be delighted to again recognize his fascinating and eternally informative style of teaching, which, because of his diligence and meticulous attention to detail, prompted many of them to become internationally famous.

The senior author, one of our most esteemed peers, postulates in closing this monograph, that "The useful life is a happy one and one of Earth's greatest blessings. Why wish for more? To make a maximal effort to extend life into a period of cheerless gloom and regret appears to be at cross purposes with societal designs for a meaningful and satisfying life for all. May not such individuals be permitted to decline acceptance of a continued vegetative existence?"

Carl O. Rice, M.D.
Editor Emeritus

Editor's Notebook

". . . power, finances, and government, and rather less about the humanistic aspects of medicine."

> *"And this was the reason why most maladies evaded the physicians of Greece – that they neglected the whole on which they ought to spend their pains, for if this was out of order it was impossible for the part to be in order."*
>
> **Plato, *Charmides***

A good editor keeps a finger to the wind, a nose in the air, an eye on the ball, and an ear to the ground. I do not possess the acrobatic dexterity to perform all these feats at once. So I resort to another technique. I keep my senses alert and open by sending copies of *Minnesota Medicine* to a handful of out of state friends, ten to be precise. These friends tell me what they think, and they tend to look at my problems with a detached, objective, and often wry eye.

A Letter from the South

Two weeks ago, a friend, Doctor Martin Netsky, a distinguished Professor of Pathology at Vanderbilt University School of Medicine, wrote a letter in response to my May editorial, which was my annual editorial report to the House of Delegates of the Minnesota Medical Association.[1] If you recall that report, I was asking the House of Delegates for $10,000 more than the Finance Committee recommended. I was also saying that perhaps the pendulum of organized medicine had swung too far towards politics and too far from science. I gently suggested the journal finances ought to be slightly adjusted (from five to six percent of the Association's total budget) to reflect this swing.

Martin's letter read, in part:

> "I want to thank you for sending "MINNESOTA MEDICINE" regularly to me. Your editor's report was interesting in that it gave me some idea of the problems you face. A few of us here were having a discussion over coffee about the problems of state journals, and the general agreement was that eventually they would have to enter into consortia to survive, just as many small colleges have done.

"I cannot forego this personel note. I enjoy your editorials, and often use them as source material for interesting discussions. *They seem, however, to be concerned about power, finances, and government, and rather less about the humanistic aspects of medicine.*" (italics mine)

His letter went on to say state journals ought to stress humanism rather than science because state journals cannot compete scientifically with national journals. I do not completely agree with his last point because our readers, according to our questionnaires, want to publish scientific material in MINNESOTA MEDICINE and want to read the scientific work of other Minnesotans in the state journal.

A Shift in Emphasis

Nonetheless, when I read Martin's letter, a bell clanged in my head. For my sensory organs had been getting other signals that Minnesota physicians want this journal to stress again medicine's traditional concerns — the dignity, worth, and well-being of the human spirit and the cultural aspects of medicine. Humanism, after all, is nothing but a doctrine, attitude, or way of life centered on human interests, hopes, and ideals. At medicine's highest level, a certain nobility of purpose exists.

Physicians, I find, once more have a yearning to be known as purposeful men and women of knowledge, rather than as worldly politicians. Perhaps there is something to this new yearning. For knowledge is the only true and distinctive resource physicians have. Politics and money and technology — as essential as they are — do not convey distinction. What conveys distinction is our knowledge, the ability to mobilize it, and the judgment to apply it.

These seismic signals of shifting emphasis were amplified at the recent meeting of the Minnesota Medical Association in St. Paul. When my Editor's Report was submitted to the reference committee, political powers within the organization spoke against my request for more money. They indicated, as was their prerogative, that physicians must "choose priorities." The implication was plain that politics and political leveraging had the higher priority. Reference committee members had different priorities. They decided to increase MINNESOTA MEDICINE's budget.

Politics and Freedom

This was a difficult decision for the committee to make. For if we doctors ignore power, finances, and government, our freedoms — to pursue a chosen specialty, to choose a place to practice, to select an appropriate fee, and to care for patients in a way we feel is professionally, humanistically, and scientifically proper — will vanish. Protecting these freedoms demands a highly disciplined, well-financed, and time-consuming political effort. These freedoms are inter-dependent. Destroy one, such as the ability of hospital based specialists to negotiate their means of compensation, and you destroy the others. Economic freedom is closely and inextricably linked to political freedom, as two recent Nobel Prize winners in Economics, Milton Friedman and Friedrich Hayek, have reminded us.[2,3]

I concur with WALL STREET JOURNAL editors, who advanced these interpretations of Senator Kennedy's latest national health proposal:[4]

> "Senator Kennedy has not quite proposed conscription. But his latest national health scheme does not fall so far short of that. The government would "negotiate" — read it "dictate" — the fees doctors and hospitals would charge. In effect, the health care industry would finally come under the total control of the federal government."
>
> And:
>
> "In short, Mr. Kennedy seeks to eliminate the necessity for Americans to make an economic choice when they utilize health services. And the burden of this bright freedom will be borne by the people who provide the service, who will have their own economic freedom sharply curtailed."

Not Everything

And yet, power, finances, and government are not everything. When the reference committee voted to grant MINNESOTA MEDICINE its request for an increased budget, they were saying something. They were indicating knowledge, science, and humanism share the platform and are part of Medicine's agenda.

Richard L Reece MD

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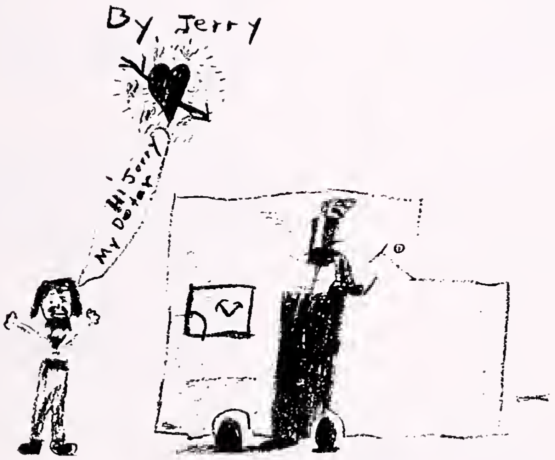

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Candidacy

Robert T. Kelly, M.D.

Dear Doctors:

Bob Kelly, after a long career in medical affairs in the Range County Medical Society, the Minnesota Medical Association, and the AMA, has agreed to be a candidate for the Board of Trustees of AMA.

In Minnesota, Bob has been President of his Medical Society on the Iron Range, President of the Minnesota Medical Association, a Trustee of that group, and President of the North Central Medical Conference. Along the way in his state he has held offices in, or chaired, nine hospital, county or state organizations. Primarily he has been concerned with ways good medical care may be provided within the framework of a pleuralistic practice system. He has taught as a clinical instructor in the Department of Family Practice of the University of Minnesota Medical School. He has been active in the difficult arena of industry and union negotiations concerning health care coverage of steel workers and iron miners in northern Minnesota.

As to the American Medical Association, Bob has served as an Alternate Delegate and then as a Delegate for twelve years in the House. He has chaired our delegation. In the House, you have observed his fair and tempered participation in even the most contentious reference committee activities. He was elected to the Council on Medical Service in 1974. He was recognized there for his leadership by being elected successively Vice-Chairman and Chairman of that Council. He headed an ad hoc committee on PSRO of the Council. He is a member of the National PSRO Advisory Council. He served on the AMA Speaker's Bureau. For the Board he has chaired the Ad Hoc Committee on Practice Evaluation.

I have known Bob well and have admired his boundless energy and his ever fair consideration of elements in our Association's activities. Throughout this stress he has remained a gentleman in every respect. To support him is a privilege. I sincerely hope that you, too, can support his candidacy.

Haddon Carryer, M.D.
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Editorials

1979 — Beyond Forgiveness?

"All children are special. There is hardly a child without some gift worth developing and each child's contribution should be celebrated with much rejoicing."

Sam Levenson
in *Say It Again Sam*

NINETEEN SEVENTY-NINE celebrates the International Year of the Child; when 137 nations will join together in recognition of the basic rights of survival for the younger members of our human race. In the last quarter of the Twentieth Century we have begun to reconsider the child as an essential resource perhaps worthy of identity. The record of this anxious and uncertain century has been abominable with regard to the world's children. One hundred or more major conflicts have taken the lives of millions of pediatric age members of humanity. At least three incomprehensible manifestations of genocide and innumerable periods of famine and starvation have added to this distasteful arithmetic. The morbidity in crippling and psychosocial consequences can never be measured.

Failure to apply basic concepts of nutrition, preventive public health measures, education, parenting and compassion have begun to tear at the foundations of all civilizations. The political ramifications of the unmet commitments to the needs of our young are beyond comprehension. The unrest, neglect, ignorance, disease, hunger and filth experienced as childhood in the squalor of an American ghetto, a refugee camp or in the aftermath of a battlefield for some ethereal ideology, breed the contemporary social discontents of terrorism, fanaticism, recidivism, and the innumerable other transgressions, which nurture an unrelenting and potentiating cycle to its inevitable conclusion.

In an era concerned with the conservation and preservation of resources, we must not fail to recognize the most important and precious of all. Childhood is a non-renewable resource. Though not all are created equal, and certainly not perfect, there is a unique and special potential in each which must be nurtured, treasured, loved and guided within the full capacity of those who bear this unique and immense responsibility. If it is the mission of the child to offer up its individuality, it is the obligation of adulthood to honor this obligation and deliver each innocence to its complete self fulfillment.

All the hopes and dreams, aspirations and victories, illusions and promises of each generation can be renewed again by commitment to those who inherit the next. To fail our progeny is to betray the past and abandon the future.

Among the most universal and pervasive maladies of world society today is violence. The roots of human destructiveness are as yet unclear, but no doubt they are linked to those of self identity. This may well be a learned process and therefore capable of significant modification. The unencumbered and assisted fulfillment of individual aspiration, by which a child is delivered to its potential, may provide the alternative to aggressive expression both individually and collectively. The process of this delivering is parenting and its multiple role models.

Our value structures are too inflexible for the developing mind. Adult chauvonism is the order of the day and childs' rights are submerged in a veil of adult hyperauthoritarianism. It is the role of the senior members to dictate rather than listen, and unfortunately also not to feel or perhaps even see. Western society is not child oriented.

Those concerned with the health care needs of children must be ever conscious of their commitment to this process of deliverance. Institutions in which these needs are met, must avoid the pitfalls of the greater community and become models for potential fulfillment.

This compendium of pediatric potpourri was conceived and compiled by inspired and well meaning adults who have at moments been rewarded with the opportunity to listen in and catch a short glimmer of that too soon forgotten megacosm called childhood. We hope in some small ways our visits are not transgressions and we can assist in the search for the secrets each child carries within itself.

David Raoul Brown, M.D.*
Guest Editor

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*Chairperson, Department of Medicine Minneapolis Children's Health Center

The Fruition of a Dream

A CHILDREN'S HOSPITAL is a unique concept but hardly a new idea. Minneapolis Children's Health Center began as a grass roots movement by parents and physicians concerned about advocacy for children. Now almost 40 years later we stand on the shoulders of those whose only resource was commitment to a dream. Idealists they were and idealists they remain, recognizing the fundamental importance of children and family to our community. The guiding principle remains simple; we want to do what is best for children. From a visionary board of trustees to committed employees and volunteers, the welfare of children is held central. Our professional staff has flourished in this humane environment and it is our hope that Minneapolis Children's Health Center may become an even more effective platform for the advocacy of child related causes. We also hope that our institution can embody the highest standards of the medical profession and reflect the humanity of our society by ministering to those who are most vulnerable — children.

Daniel J. Whitlock, M.D.*
Chief of Professional Staff

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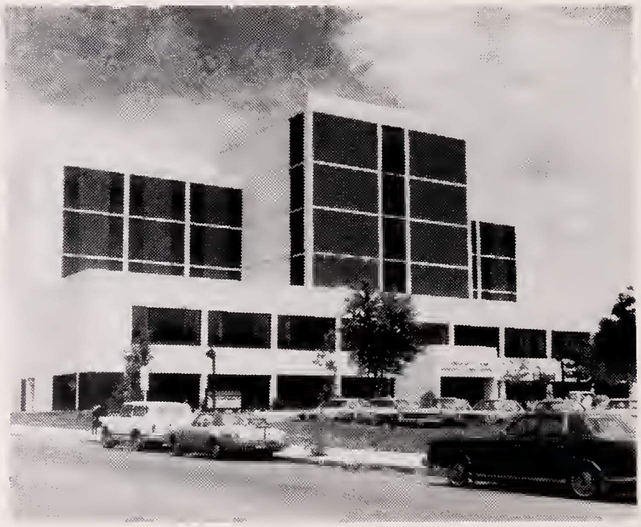
*Children's Health Center, Minneapolis.

Cover Drawing

"Children's Health Center: It's a Great Year for Kids! 1979"

Andrea Brown is the 8-year-old daughter of a Children's Health Center pediatrician and frequently accompanies her daddy to make rounds and see sick children. Her drawing commemorates the coming of spring and her positive feelings about the hospital. It also considers 1979 as the International Year of the Child as a great year for kids.



Children's Health Center-Minneapolis

Anterior Cranial Vault and Bony Orbit in Infancy

Craniofacial Surgery

BRUCE B SHILLING, M.D., PH.D.,* ERICH S. WISIOL, M.D.,* BROOKS J. POLEY, M.D.,* THOMAS W. PURCELL, M.D.*

Embryologic defects of the anterior cranial vault and contiguous orbit present as distortions of the forehead and upper face. Surgical osteotomies and skeletal repositioning should be accomplished before one year of age. The corrections of the deformities, nasal encephalocele and plagiocephaly, are discussed and illustrated.

RECENT ADVANCES IN craniofacial surgery are now applied to the growing bony tissues of the anterior cranial base and upper facial skeleton. Craniofacial dysostosis, as described by Tessier,[14] is defined as premature synostosis of the cranial sutures associated with facial deformities. Many surgeons, Edgerton, et al;[2] Hoffman and Mohr;[4] Whitaker, et al;[17] McCarthy, et al.;[9] and Tessier,[16] advocate the early surgical intervention, before one year of age, for the treatment of bony dysostoses of the cranial base and contiguous visceral skeleton. These advocates perform a linear coronal craniectomy as well as selective osteotomies of the other cranial and facial stenotic sutures, those sutures between the visceral skeleton and the cranial base, in order to take advantage of the rapidly expanding frontal lobe of the brain and ocular globe. In the first year of life, the growth of these two organs, with the concomitant and expansile force, advocated by Enlow,[3] approaches nearly forty-five percent of the final adult weight. The purpose of this paper is to describe these most recent craniofacial surgical principles as they apply to the anterior cranial vault and orbital bony tissue in the correction of a four and a half month old boy presenting with a nasal encephalocele, a two and two-thirds year old girl with a similar deformity, and a four and a half month old male presenting with a right craniofacial plagiocephalic dysostosis.

Review of the Embryology of the Face and Anterior Cranial Vault

In the 20 day embryo a neural tube is present. This neural canal remains open at the anterior posterior neuropore, but both eventually close in the second half of the fourth week.[10] The ectoderm, which forms this primitive nervous system, gives rise to underlying mesoderm, from which skeletal muscle and connective tissue arise. This mesoderm migrates, subepidermally, in clusters of cells comprising the facial processes before undergoing the final differentiation.[5] This dynamic role of the mesenchyme is important in the development of the normal base of skull and facial skeleton. Any disturbance in the proliferation, migration or differentiation results in abnormal development.[13] Malformation in the area of the midline of the face, resulting from faulty development of the nasomedial or nasolateral processes, results in a variety of abnormal conditions.[8] Delay of closure of the anterior neuropore may leave the surface ectoderm remaining in contact with the underlying dura. This presents, at birth, as a dermoid cyst, teratoma, or frontal encephalocele. The basis for the deformity, however, lies in the mesodermal deficiency or its faulty migration. The resultant defect is a broad nasal vault, often associated with a cleft. The brain may herniate through the bregmatic portion of the frontal bone with subsequent concomitant hypertelorism. As the developing optic vesicle commences migration from its lateral position, the medial position is halted by the interposed brain. This arrest results in clinical hypertelorism with laterally positioned medial canthi.

Growth at the base of the skull commences from the cartilaginous skeleton with centers of calcification. These coalesce to form the adult structures of the ethmoid and sphenoid bones. Membrane bone commences in the mesenchyme; coalescence of these centers of ossification form the adult zygomatic, maxillary, lacrimal and frontal bones. Thus, abnormality at the cranial base will necessarily result in upper facial deformities.[6]

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*Active-attending staff of Children's Health Center of Minneapolis. Each speciality is as follows: Shilling, plastic surgery; Wisiol, neurosurgery; Poley and Purcell, ophthalmology.

Theories of facial growth are not agreed upon; however, that described by Enlow[3] is widely accepted. The rapidly expanding neurocranial forces, the frontal lobe of the brain and ocular globe, exercise great expansile pressure on the embryonic and newborn cranial base and facial skeleton. According to Boyd,[1] growth of the frontal lobes is approximately 30% of the adult mass by six months of age. At one year, the growth has proceeded to 45% of the adult mass; and at two and three years of age the mass is 55% and 65%, respectively. The growth of the ocular globe is very similar to that of the frontal lobe with doubling in size at the end of the first year of life and obtaining its near adult size by three years of age. Premature stenosis at the cranial base or in the orbital sutures produces a vertical sloping orbital roof with the reduction in the orbital volume and extrusion of the ocular globe (exorbitism). This theory is further supported by the histologic demonstration of absent sutures and radiologic evidence of premature sutural closure.[11] Failure of expansion of the coronal suture in continuity with the frontosphenoidal and frontoethmoidal dysostoses comprise the classical findings in Crouzon's dysostosis. This is frequently combined with sphenozygomatic sutural stenosis. The exorbitism is obvious. The flat retracted brow and forehead are prominent.Malar eminences are flat and the mid-third of the face is retracted. If the premature synostosis is unilateral (plagiocephaly), the forehead and brow are retracted on the involved side with compensatory overgrowth of the contralateral forehead presenting a bulge with a grossly lopsided calvaria. The retraction of the lateral orbital rim and malar eminence appear on only the involved side with ipsilateral exorbitism.

Discussion

The congenital deformity of frontal encephalocele was recently reviewed by Mazzola.[8] In 235 congenital malformations of the nasal and frontal area, eleven were encephaloceles. Obligatory hypertelorism as well as the herniated brain was found in all cases. Indications for neurosurgical repair have been well established.[7] Aside from the obvious cosmetic improvement, resulting from the excision of the herniated silent neural tissue, protection of the brain with an aloplastic or homographic material has been the accepted method and goal of the repair. Tessier[14] advocated additional selective osteotomies about the medial and lateral orbital rim in an effort to correct the concomitant obligatory hypertelorism. Such osteotomies, carried out during the first year of life, but at the same time as the craniectomy and dural repair, allow the rapidly expanding frontal lobe of brain and ocular globe to remodel the orbital rim structures and orbital volume. Medial movement of the orbital rims also corrects the deficit in the bregmatic portion of the frontal bone, the embryologic deficient mesenchyme. Unilateral premature craniofacial stenosis classically presents as plagiocephaly. The cosmetically devasting deformity is that of asymmetry of the facial skeleton and forehead with ipsilateral exorbitism. The patient may present with the inability to achieve ocular fusion. This is presumably due to abnormal orbital volume and rim position. Exposure keratitis secondary to exorbitism may be a problem. Simple linear coronal craniectomy corrects slightly over 50% of the facial asymmetry,[12] but generally produces a more symmetrical calvaria, if carried out before one year of age. Advancement of the craniectomy to include the premature sphenozygomatic synostosis has recently been advocated McCarthy[9] and Whitaker.[17] Hoffman and Mohr[4] as well as Whitaker[17] advocate a complete advancement of the entire orbital rim by pivoting the rim and orbital floor on the medial wall, in the area of the lacrimal fossa. This advances (in the anterior-posterior plane), the lateral orbital rim and effects a rapid expansion of the orbital volume.

Case Reports

Case 1

The patient is a four and a half month old male, the product of a normal pregnancy, labor and delivery. At the time of delivery, a mass was noted over the bridge of the nose. The diagnosis of a frontal encephalocele was tendered (Figure 1). Hypertelorism was present. Examination revealed a 2½ X 3 cm. mass, firm in consistency, lying over the glabellar region of the nose. This mass became blue when the infant cried. The mass was not pulsatile. Consultation with the radiologist revealed the bregmatic frontal bone deformity to measure 2 X 2½ cms. The cribriform plate was depressed 1½ cms. Tomograms revealed the superiomedial aspect of the orbital rim to be deviated laterally approximately 8 to 9 mms. This produced a medial canthal displacement, laterally of 2 to 3 mms. Compared with infants of a similar size and age, the intercanthal space was widened 4 to 5 mm. Preoperative dissection of a dried skull recreated a bregmatic deformity and the lateral displacement of the medial-superior orbital rim (Figure 2). Through a coronal scalp incision the herniated portion of brain (Figure 3) was excised after removing the calvaria. A strip of bone across the brow was allowed to remain intact. The dura was repaired. The actual bregmatic deficit measured 1.7 cms. in diameter. Selective osteotomies were carried out so as to rotate the superio-medial orbital rim toward the midline, pivoting at the lacrimal fossa. The lacrimal sacs were retracted and 2 mms. of bone was removed just medial to the anterior lacrimal crest. Bilateral bone flaps, hinged inferiorly in the area of the lacrimal duct, were carried medially (Figure 4). The bregmatic deformity resulting after closure was a triangle approximately 4 mms. on edge. The bony deficits were in the roof of the orbit. The medial canthi were repositioned and the excess skin of the nose was excised by a Z-plasty. The postoperative course was unremarkable. The postoperative result produced a correction of the hypertelorism, protection of the brain in he bregmatic area with no apparent neurologic deficits (Figure 5). Subsequent radiological examination, 6 months postoperatively, evealed calcification in the area of the selective osteotomies as well as in the donor area of the orbital roof.

Case 2

The patient is a 2 9/12 year old female. This girl was adopted by a Minneapolis family such that the facts of her earlier life are unknown. The patient presented with a 2½ cm. wide, 1 cm. elevated regmatic mass, soft to palpation, which became accentuated when he child cried (Figure 6). Polytomography and computerized omography revealed a 2½ cm. deficit in the midline frontal bone. Ophthalmologic examination documented 10 prism diopters of esotropia. At the time of surgery, utilizing the approach similar to that of Case #1, the herniated brain was resected. This did not involve the cribriform plate, olfactory bulbs, or optic nerves. The 2 cm. dural defect was repaired. Selective osteotomies were carried out. Wedges of bone, 4 mm. in width, were removed just medial to the medial canthi, bilaterally. Medial rotation of the bone flap, based at the lacrimal fossa, produced 12 mm. of deficit in each orbital roof. No bregmatic deficit of bone was present after rotation of the flaps. The excess skin was removed by a Z-plasty. The six months postoperative presentation (Figure 7) is acceptable.

Case 3

The patient is a four and a half month old male, the product of a normal pregnancy, labor and delivery. At birth, asymmetry of the facial and frontal skeleton was noted. Over the ensuing months the asymmetry became more pronounced (Figure 8). A diagnosis of plagiocephaly was established. Radiologic examination revealed the classical coronal sutural thickening on the right side (Figure 9). Binocular vision was absent. Physical examination revealed a

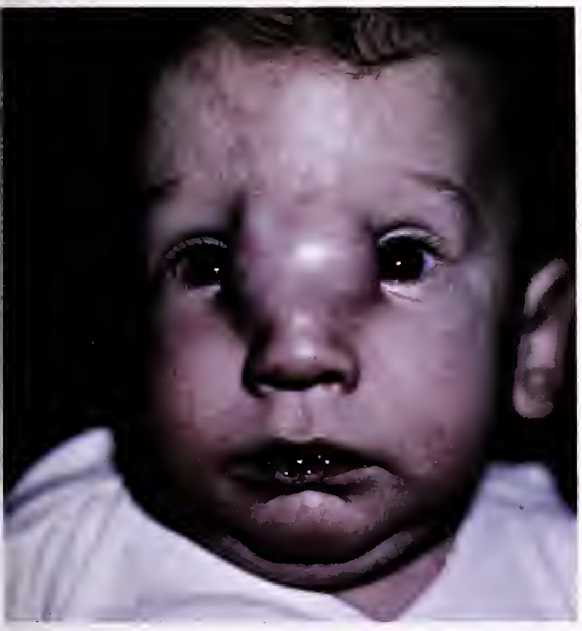

Fig. 1 — Nasal encephalocele in four and a half month old male. (By permission.)

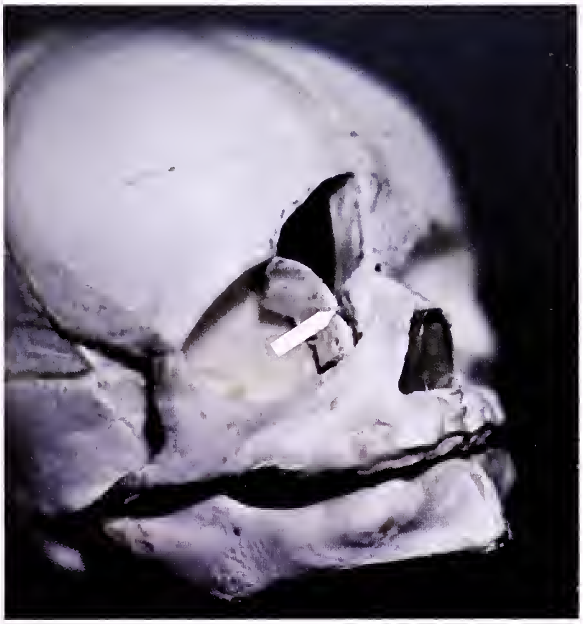

Fig. 2 — Bregmatic deficit of frontal bone with lateral displacement of contiguous orbital rim secondary to the progressively expanding neural tissue in the encephalocele; lateral displacement of the medial canthi (arrow).

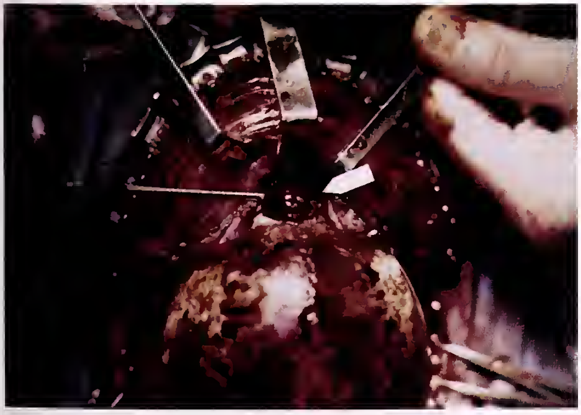

Fig. 3 — Encephalocele, at surgery (arrow).

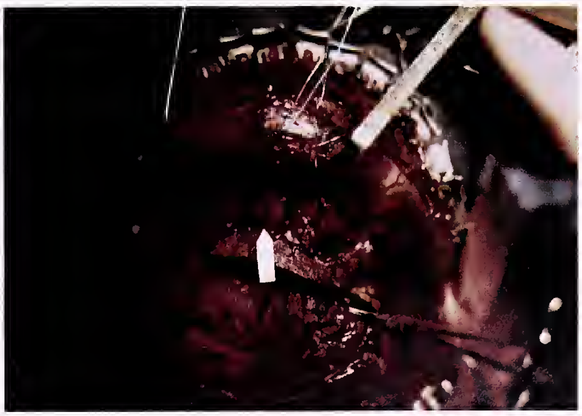

Fig. 4 — Medial rotation of orbital rims accomplished with minimal resultant deficit (arrow).

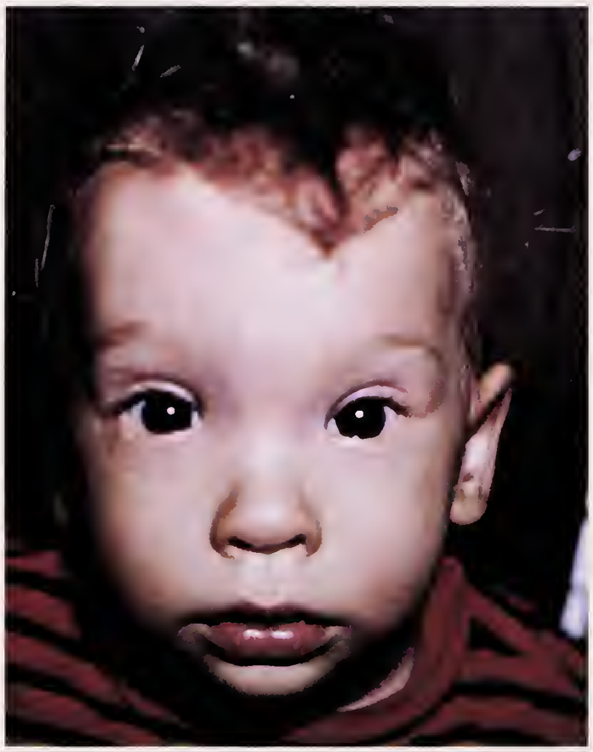

Fig. 5 — Postoperative result at six months. (By permission.)

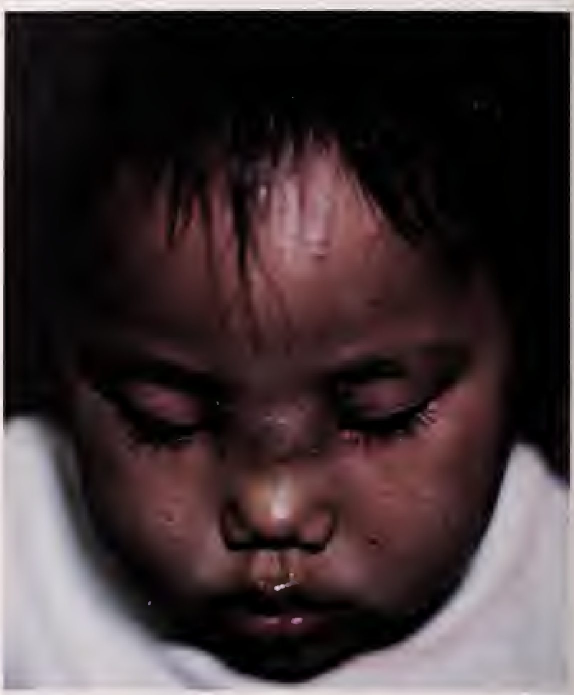

Fig. 6 — Nasal encephalocele in 2 9/12 year old female (oriental population carries higher incidence of the deformity). (By permission.)

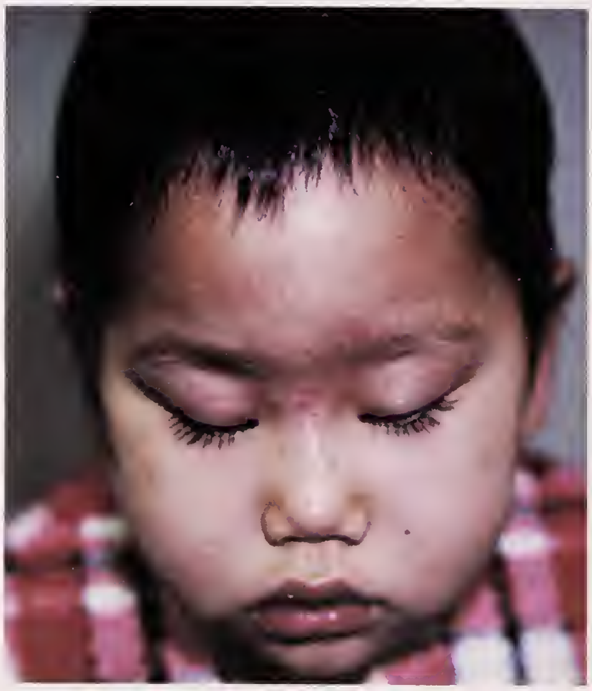

Fig. 7 — Postoperative result at six months. (By permission.)

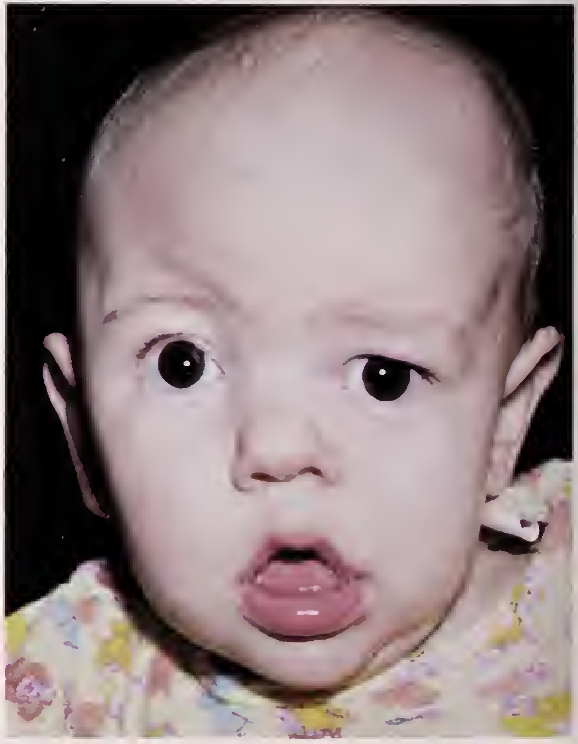

Fig. 8 — Right plagiocephaly in four and a half month old male. (By permission.)

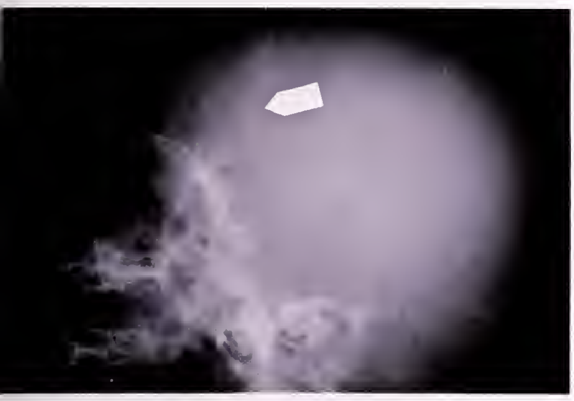

Fig. 9 — Radiologic demonstration of coronal premature ynostosis (arrow).

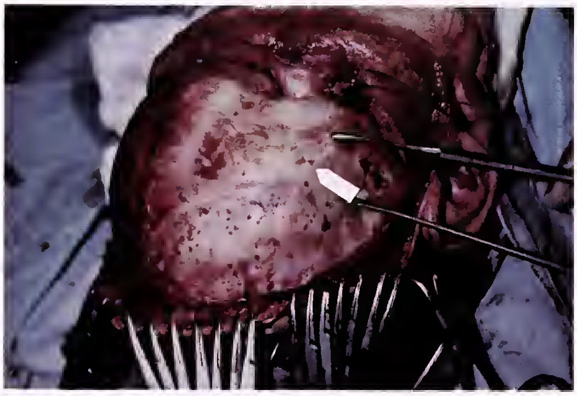

Fig. 10 — Coronal dysostosis, at surgery (arrow), which continues into sphenozygomatic suture.

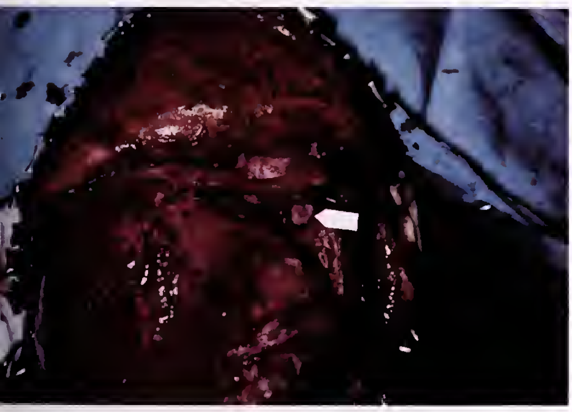

Fig. 11 — Stabilization of advanced orbital rim by bone graft arrow) in released sphenozygomatic dysostosis. (By permission.)

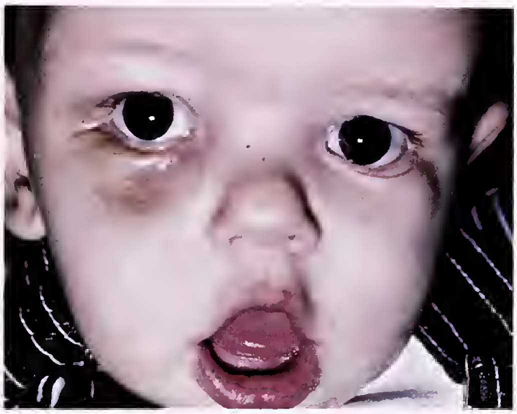

Fig. 12 — Postoperative result, eight days, with advancement of orbital rim. (By permission.)

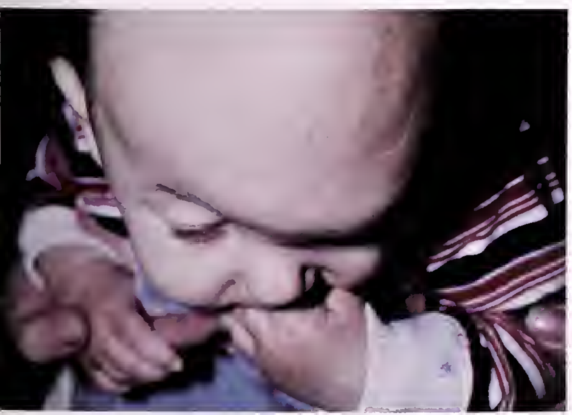

Fig. 13 — Preoperative brow view. (By permission.)

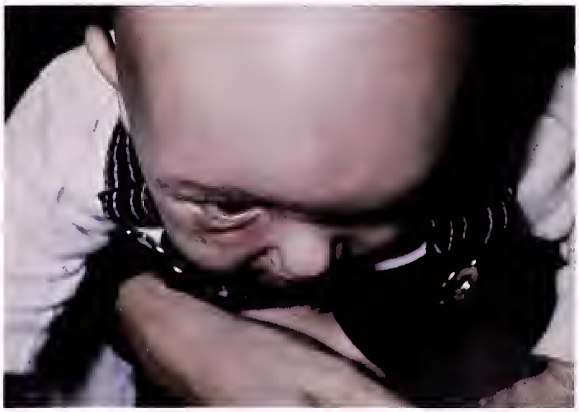

Fig 14 — Brow view, eight days postoperatively, demonstrating near symmetry of orbital rims; advancement of right forehead progressed over ensuing months.

retropositioned right lateral orbital rim (as if growth had been prevented in the area of the frontal-zygomatic suture and decreased as one progressed centrifugally from the suture). There was sloping of the right forehead with depression of the brow and a compensatory bossing of the left forehead. Preoperative laboratory dissection of a skull reproduced the deformity of this patient. This reconstructed skull demonstrated a contracture at the coronal suture as well as the frontosphenoidal, frontoethmoidal and sphenozygomatic sutures. Correction of the forehead deformity by excision of the stenotic coronal suture (Figure 10) created a bone flap, based medially at the metopic suture. By selective osteotomies at the dyostoses above as well as the orbital floor the entire orbital rim could be advanced forward. This was stabilized in position by a wafer of bone taken from the calvaria during the linear craniectomy (Figure 11). All surgery was carried out through a coronal scalp and subciliary incisions. Postoperatively (Figure 12), the course was unremarkable. The patient was noted to fuse his gaze approximately one week postoperatively. This has continued to remain fused. The anterior advancement of the lateral rim remains stable (compare preoperative position, Figure 13, with postoperative position, Figure 14). Over the ensuing months, the right frontal bone advanced slowly. The near symmetrical position of the orbital rims has remained. The child demonstrates no neurologic or ocular deficits.

Conclusion

Craniofacial anomalies of the anterior cranial vault and bony orbit often present a need for surgical intervention. No longer do the parents of these infants need to be told that nothing can be done. The parents need not be told that the patient will grow out of the situation only to watch the deformity progress or at best not correct itself. The approach of the deformity, be it a premature synostosis, tumor (including encephalocele), midline cleft, or classical oblique facial cleft, should include all the classical goals of neural and facial surgery. But new advances allow the surgical release of stenotic sutures and repositioning of the orbital rim. This is carried out preferably before the patient reaches 12 months of age. With subsequent growth of the frontal lobe of the brain and ocular globe, the anterior cranial base and orbital skeleton are expanded and molded by natural remodeling forces; thus a more nearly normal and acceptable facial and forehead skeleton is produced. This requires a team, initiated by the pediatrician, which includes an anesthesiologist, radiologist, ophthalmologist, neurosurgeon and plastic surgeon. The risk and postoperative care is similar to any craniotomy and mid-facial fracture.

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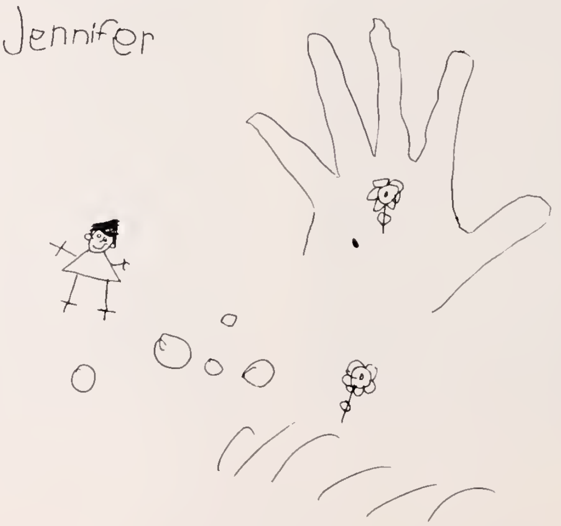

Advances in Oral-Facial Deformity Reconstruction

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The multidisciplinary team concept of treating a wide variety of oral-facial deformities at Children's Health Center has resulted in correction of a variety of deformities, frequently untreated in years past. The team consists of the Pediatric Surgeon, Oral Surgeon, Pediatrician, Pedodontist, Orthodontist, Anesthesiologist, Ophthalmologist, Otolaryngologist, Psychologist, and other disciplines.

Primary repair of cleft lip and palate, mandible prognathism, facial fractures and related deformities has now been expanded to include reconstruction utilizing bone and skin grafts in both the maxilla and mandible, nose, and peri-orbital areas. Cleft maxillas are repositioned and bone grafted to restore normalcy. Mandibles and maxillas are repositioned in any dimension to restore facial and dental harmony and function. Youngsters with such abnormalities achieve a sense of restored well-being after undergoing these procedures.

NEW SURGICAL TECHNIQUES and the multidisciplinary team concept of treating oral-facial deformities at Children's Health Center have resulted in correction of a variety of deformities, frequently untreated in years past. The team consists of the pediatric surgeon, oral surgeon, orthodontist, pediatrician, dentist, anesthesiologist, ophthalmologist, otolaryngologist, psychologist, and frequently other disciplines. The facial deformities treated are the result of congenital defects, e.g. cleft lip and cleft palate, hemifacial microsomia, Treacher-Collins syndrome, etc.; developmental defects, e.g. mandibular prognathism, mandibular retrognathism, etc.; and residual traumatic defects, e.g. non-union or malunion of fractures of facial bones. The consequences of these deformities are often facial disfigurement and severe malocclusion of the teeth. These esthetic deficiencies and functional impairments are the presenting needs for surgical correction.

Although many attempts have been made to correct a variety of these defects in years past, the amount of correction was limited by lack of technology to mobilize bones in the maxilla and upper face successfully and safely. Early surgical attempts to correct cranial-facial and mid-facial deformities resulted in poor post-operative results and high morbidity to either the patient or the parts mobilized. Since 1950, Tessier[1] in France and Obwegeser[2] in Switzerland have pioneered some beautiful and highly successful surgery through their daring and innovative concepts. Epker,[3] Bell,[4] Wolford[5] and others have greatly expanded and refined these techniques developing surgical approaches for the correction of a variety of mid-facial deformities which can now be undertaken with a high degree of safety and predictably fine end results.

Because of the developments in the last fifteen years, primary repair of cleft lip and palate, mandibular prognathism, facial fractures and related deformities, surgery has now been expanded to include reconstruction of all facial bones utilizing bone, skin and alloplast grafts where necessary. Cleft maxillas are repositioned and bone grafted to restore continuity and alveolar ridges. Mandibles and maxillas are repositioned in any dimension to restore facial and dental harmony and function. Youngsters with these abnormalities corrected achieve a sense of more complete rehabilitation after undergoing these procedures.

Successful correction of any oral-facial deformity can only result if first an accurate diagnosis of the condition is established. To establish the appropriate diagnosis examination is augmented with a variety of

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radiographs including the panographic Xray, cephalometric lateral head Xray, a series of photographs of the face and dentition, plaster of paris moulages of the face when appropriate, and plaster of paris models of the dental occlusion. In certain types of deformities, particularly the congenital defects, genetic counseling becomes a part of the treatment plan to inform parents and afflicted individuals of the probabilities of further occurrences in future generations. Treatment planning includes a detailed analysis of Xrays, photos and models. Mock surgery is frequently performed on models to aid in accurate prediction of surgical limits and results. In more complicated cases, staging of the corrective surgery is often necessary to achieve the desired end result.

Case Reports

The following case reports illustrate a few of the advances developed by the team approach.

Case 1

This eight-year-old male was born with bilateral cleft lip and cleft palate with the primary lip and palate repairs accomplished during the first one and one-half years of life. Persistent oral-nasal fistulae and a mobile pre-maxilla were a source of masticatory disfunction and a slight hygiene problem for the youngster. The escape of air into the nasal cavity occasionally resulted in hypernasality with certain speech sounds.

Review of dental radiographs and examination indicated that this boy would benefit from an iliac bone graft to stabilize his freely moveable pre-maxilla and close the oral-nasal fistulae. The appropriate chronological age at which to do the grafting was determined from dental radiographs and the position of the developing tooth buds. This youngster was considered ready for grafting at this particular time because of the dental relationships.

This boy was admitted to Children's Health Center on February 14, 1977 and on the following morning the graft procedure was accomplished. Admission physical examination and laboratory studies were within normal limits. While the oral surgeon repaired the fistulae and prepared the subperiosteal beds in the alveolar cleft defects for reception of the bone graft material, the pediatric surgeon was harvesting bone from the right iliac crest. This double-teaming with the multidisciplinary team cut the operating time in half reducing greatly the anesthesia time and to some extent the morbidity of the procedure.

Repair of the alveolar defect included closure of the nasal-oral fistula by first creating a new nasal floor about the alveolar defect. Bone fragments were packed on the bared lateral and proximal defect walls wedging segments in to stabilize the mobile pre-maxilla and packing the nasal floor up to the maximum height to help support the alar bases. Pedicle flaps from the labial buccal vestibule were then elevated consisting of full thickness mucoperiosteum and rotated to cover the grafted bone joining the pedicles at the mid-line in the palate and suturing them along the original wound margins. At the same time, bone was removed from the iliac crest in a unique manner utilizing the "trap door"[6] technique. The cortical-cartilaginous iliac crest is hinged back with cancellus bone slices measuring approximately two to three cm. in length and two to five mm. in thickness excised between the medial and lateral cortical plates with an osteotome. These wedges were placed in a canister and passed over the barrier drape for replacement in the oral cavity. The trap door lid is then replaced on the iliac crest with little or no residual deformity to the donor ilium.

The youngster was maintained on a liquid diet, prophylactic antibiotic coverage and was up and about two days following the surgery and discharged on the fourth post-operative day.

The photos below demonstrate the pre-operative (Figure 1) and the one year post-operative views (Figure 2). The post-operative view demonstrates closure of the oral-nasal fistulae and immobilized permaxilla supported by new bone, ready for the orthodontist to eventually arrange the dental units to normal occlusion. The dentist will then be able to replace the congenitally missing teeth with fixed bridgework.

Case 2

This seventeen-year-old female was born with a mandibulo-facial dysostosis known as hemifacial microsomia.[7] This congenital defect is the result of agenesis or severe hypoplasia involving the temporo-mandibular, maxillary and zygomatic elements on a unilateral basis. The pinna of the ear is redundant or totally missing, the auditory apparatus is hypoplastic or totally non-existent, the temporo-mandibular joint, condyle and ramus are hypoplastic and occasionally have experienced complete agenesis. The zygoma and maxilla on the affected side are hypoplastic, the seventh nerve has

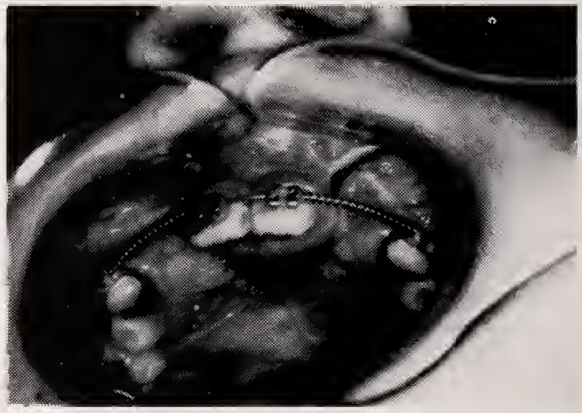


Fig. 1 — Intraoral photograph of 8-year-old with repaired bilateral cleft lip and cleft palate. Note bilateral nasogingival fistulae with alevolar arch defects and free-floating premaxilla. (By permission)

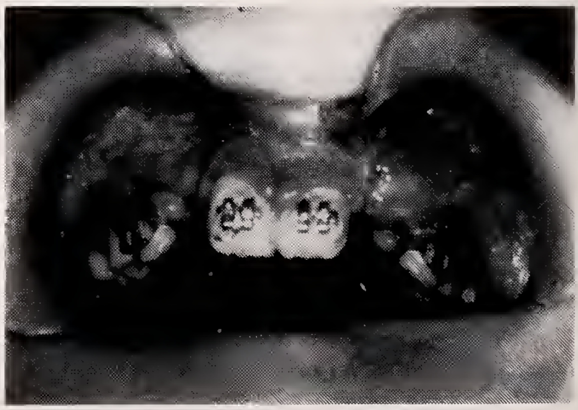


Fig. 2 — Postoperative intraoral photograph following surgical closure of nasogingival fistulae plus iliac bone grafts to stabilize the premaxilla and to augment the alveolar ridge.

reduced or non-existent function and many of the soft tissue elements are hypoplastic with the temporalis and masseter muscles frequently non-existent. The end result is severe facial asymmetry with frequently poor dental function because of the canted occlusion and malposed teeth.

Complete orthognathic records were secured in addition to careful examination and history recording. The youngster was then admitted to Children's Health Center on August 7, 1978 where on the following morning the mandible was repositioned through bilateral ramus osteotomies from a submandibular approach to reduce the severe canting and close the anterior open bite. The right maxilla was then approached through transantral and transpalatal approaches repositioning the segment from the right cuspid to the tuberosity area, dropping this segment approximately one cm. into the new occlusion. The osteotomies were stabilized with bone grafts harvested by the "trap door" technique and through the placement of interdental splints, intermaxillary fixation and direct wire fixation to the upper maxilla. The patient tolerated these procedures without untoward incident and was discharged from Children's Health Center on August 13, 1978.

Figure 3 demonstrates the pre-surgical facial asymmetry, and Figure 4 is the youngster two months post-operatively. This is an

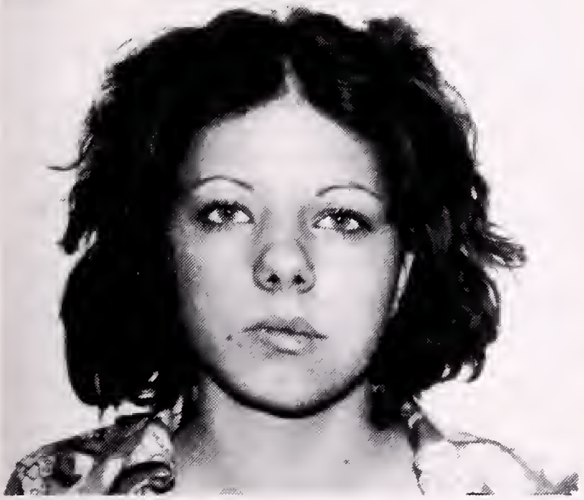


Fig. 3 — Frontal photograph of a 17-year-old with right hemifacial microsomia. Note facial asymmetry with underdevelopment of temporomandibular, maxillary and zygomatic elements. (By permission)

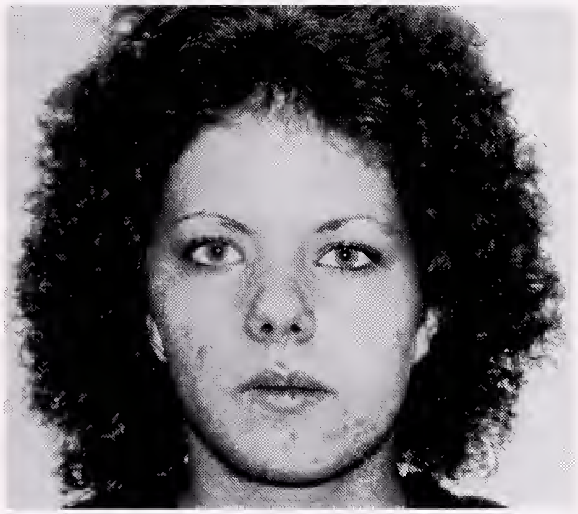


Fig. 4 — Postoperative frontal photograph following mandibular osteotomies plus LeForte I procedure to mobilize the maxillary, zygomatic and premaxillary elements to correct facial asymmetry and to realign the canted malocclusion. (By permission)

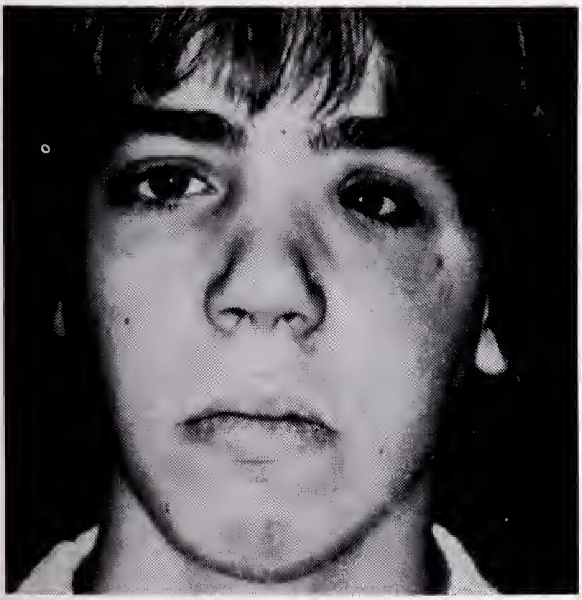


Fig. 5 — Frontal photograph of 14-year-old boy following auto accident with impacted malunited fractures of left mandible, maxilla, zygoma, orbital plate and nasal bones. Note broadened nasal bridge, unequal palpebral fissures and indented left face. (By permission)

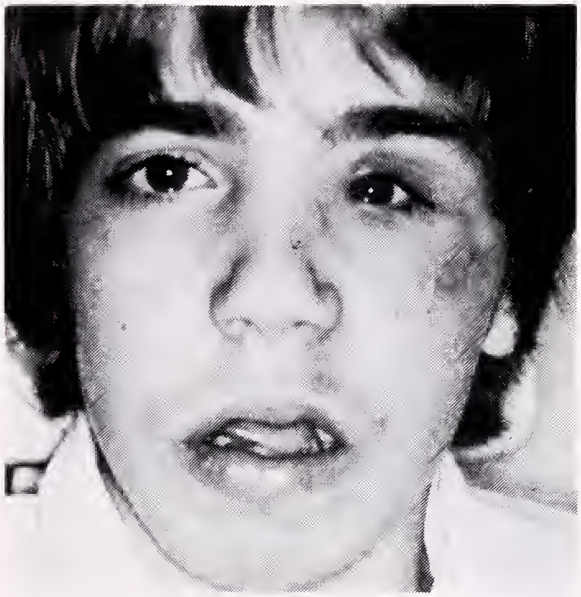
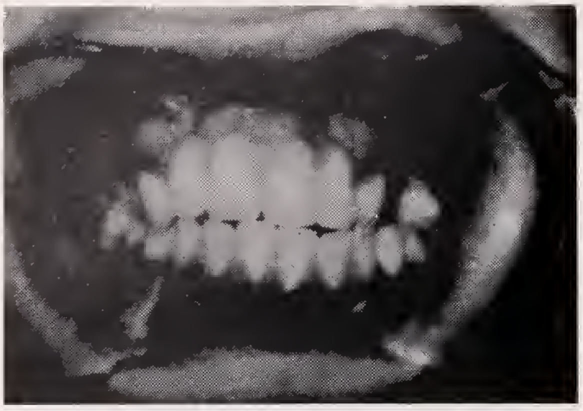
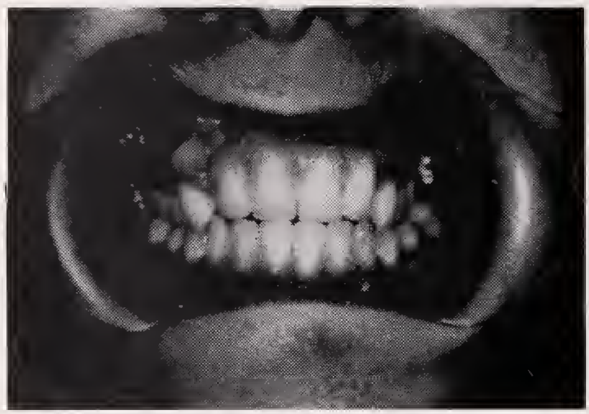


Fig. 6 — Two months postoperative photo following reconstruction of nasolacrimal duct, left zygomatic arch, left maxilla plus a LeForte II procedure to realign the maxilla with bone wedges from the iliac crest. (By permission)





Figures 7 (top) and 8 (bottom) — Intraoral photographs, pre- and postop showing malocclusion corrected following severe trauma with impaction.

example of staged surgical correction as a genioplasty will be performed in the future to further reduce the facial asymmetry. Orthodontic treatment will complete the correction of the malocclusion and is currently in progress.

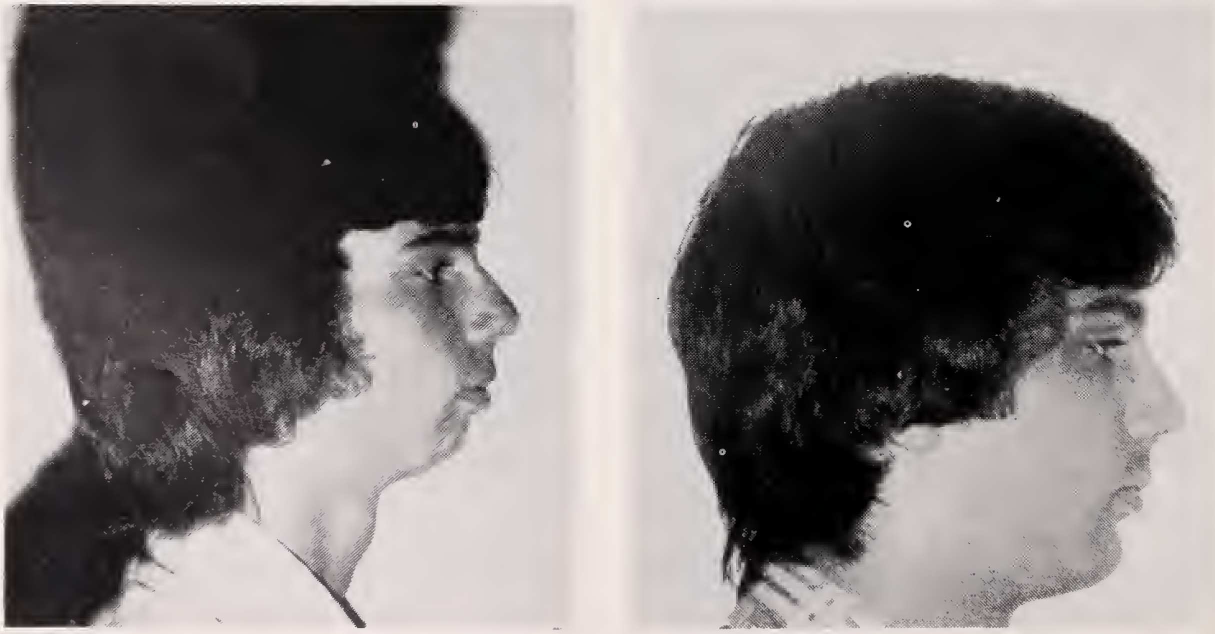
Case 3

This fourteen-year-old boy was in an automobile accident in June, 1977. He sustained multiple injuries to the maxillo-facial area, chest, abdomen, and limbs. Unconscious for approximately one month following the injury, certain treatments had to necessarily be deferred and as a result the youngster sustained a malunion of the bony structures about the left orbit including the zygoma and left maxilla. Figure 5 demonstrates the depressed zygoma and orbital distortion along with widening of the nasal bridge.

Consultations between the pediatric surgeon, the oral surgeon, the ophthalmologist and the otolaryngologist resulted in planning a staged reconstruction of the deformity of the left face. Initially reduction of excessive scarring about the left orbit was undertaken. Full orthognathic records and examination indicated that in addition to the bony deformities about the left orbit and maxilla, the youngster had diplopia in an inferior gaze, a malfunctioning lacrimal apparatus on the left and persistent deformity about the nasal bridge.

The lacrimal duct was re-established by the ophthalmologist in February, 1978. The youngster was readmitted to Children's Health Center on April 17, 1978 and on the following morning the left zygoma and left maxilla were refractured through appropriate osteotomies utilizing both an intraoral approach and incisions placed in old scars about the left orbit. The bony units were repositioned and stabilized again through appropriately placed bone grafts, dental splinting and direct bone wiring (Figure 6). The youngster was discharged from the hospital on April 21, 1978. Severe malocclusion following traumatic impaction (Figure 7) was corrected surgically.

Temporary replacement of the missing teeth was accomplished with placement of a partial denture prosthesis placed by the pedodontist six weeks post-operatively following the initial repair of the repositioned units (Figure 8).



Figures 9 (left) and 10 (right) — Profile photography of 15-year-old lad before and after surgical correction of mandibular micrognathia (By permission)

Case 4

Mandibular micrognathia or deficiency is one of the most common occurring facial-dental deformities. This fifteen year old boy (Figure 9) presented to the orthodontist for correction of the resultant severe malocclusion.

Orthognathic workup including consultation with the oral surgeon indicated that restoration of Class I dental occlusion would necessitate mandibular advancement and advancement genioplasty along with orthodontia. Physical examination and laboratory studies were within normal limits.

The patient was admitted on August 18, 1974 and on the following morning mandibular advancement via a submandibular approach and an advancement genioplasty via the intraoral approach was accomplished. The mandibular advancement was accomplished through bilateral coronoidectomies and bilateral "L" osteotomies of the rami. The patient was discharged from the hospital on August 24, 1974 and following seven weeks of intermaxillary fixation and bone repair, he had his occlusion restored orthodontically. Figure 10 is a lateral view two years post-operatively.

Summary

During the last five years, a virtual explosion of ideas and surgical techniques for the reconstruction of facial deformities has occurred. Multidisciplined teams can now provide improvement in function and esthetics to such a degree that new hope is now afforded all such afflicted individuals. A firm base has now been established on which to build. The techniques for oral-facial deformity reconstruction have just started to unfold.

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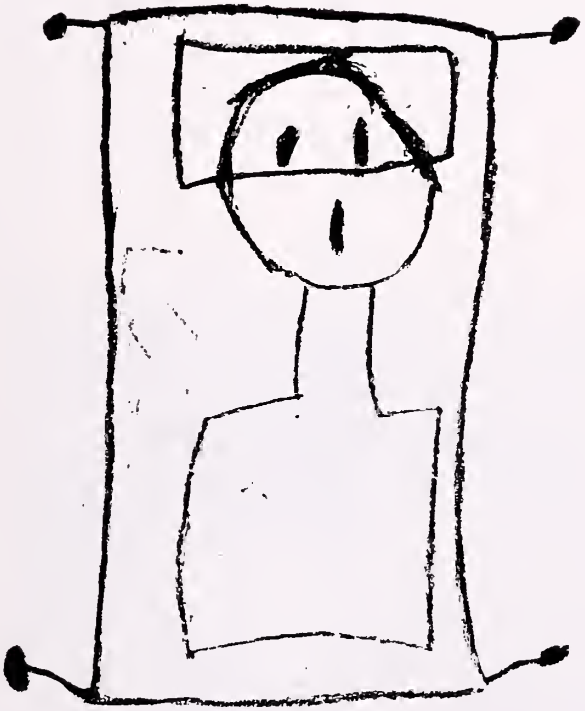

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Pediatric Cardiology at Children's Health Center
First Five Years

HAROLD KATKOV, M.D.*

The pediatric cardiology program was in the planning stages long before the hospital opened. Evaluation of the first five years of the pediatric cardiology diagnostic and treatment center from all aspects is presented. A detailed analysis of the types of services offered and critical review of the surgery accomplished is summarized. It demonstrates a well organized, smoothly functioning, inter-disciplinary team offering complete pediatric cardiovascular diagnostic and treatment capabilities in a totally equipped physical center. Availability of a multidisciplinary team of subspecialists functioning together with ward and intensive care units, in team concept, with continuous conferencing and self-analysis, has evolved. Specialized support and outreach programs are also reviewed.

PLANNING FOR a pediatric cardiology diagnostic and treatment center at Children's Health Center of Minneapolis began several years before its opening. From the onset of such planning, the basic concept was to offer, for complete cardiovascular care, a facility in a private practice setting for children of all ages. Guidelines were those first stated by the Intersociety Commission for Heart Disease Resources.[1-4] It was the intention of the original workers to bring together all aspects of diagnostic and surgical capability with a well established complete support system in the hospital with utilization of newer techniques of outreach and family support systems.

From these early plans has evolved a pediatric cardiology diagnostic and treatment center available for referral of all infants, children, and adolescents with possible heart disease who require the expertise as represented in such a center.

A fundamental operating principle is continuity of care, utilizing the patient's primary physician, the pediatric cardiologist receiving the referral (or the surgeon), and the central physical facilities of Children's Health Center and Hospital.

Specific criteria set forth by the Ad Hoc Committee on Standards for Cardiac Diagnostic and Surgical Centers[4] have been followed and fulfilled as well as following the recent Guidelines for Pediatric Cardiology Diagnostic and Treatment Centers as published by the Section of Cardiology of the American Board of Pediatrics.[5]

These guidelines include the availability, on an around the clock basis, of pediatric cardiologists, cardiovascular surgeons, cardiovascular radiologists, pathologists operating a totally equipped laboratory capable of microtechnique, and the presence of hospital services which must include a totally equipped and staffed Level III Neonatal Intensive Care Unit, supervised by certified pediatric neonatologists. At Children's Health Center a separate Life Support Unit is also a totally equipped intensive care system with specifically trained nurse intensivists supervised by physicians in the Department of Anesthesiology.

At Children's Health Center and Hospital in Minneapolis there are five active pediatric cardiologists who have formed a subsection of the Department of Medicine, so that all decision-making and planning is a departmental function. All are private practitioners available for consultation. There is a staff of cardiovascular surgeons, physician anesthesiologists trained in the field of pediatric anesthesiology, and these together with all of the support make up the team.

As the total cardiac team has evolved, a remarkable interaction, designed in anticipation, has resulted. A unified concept has occurred creating a smooth interaction of this cardiovascular team, each in support of the other for the patient's overall benefit. The relationship between primary physician — pediatric cardiologist — cardiovascular surgeon — anesthesiologist — operating room and life support nurses — has matured. This team has developed confidence in each other's capabilities. Each member of the team has evolved utmost respect for all other members. This requires a remarkable commitment on the part of everyone involved.

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Medical-Surgical-Cardiac Conferences are interdisciplinary and include pediatric cardiologists, cardiovascular roentgenologist, cardiovascular surgeons, anesthesiologist, pathologist, and members of the nursing and technical staff involved in preoperative, operative and postoperative care. This conference is most helpful in making difficult management decisions, creates a critical atmosphere in which to review cases before and after surgery, and establishes criteria for quality care. Each month, a pediatric cardiac pathology conference is directed by Dr. Jesse Edwards. In addition, Dr. Edwards is available as a consultant on individual cases.

Since the cardiovascular program relies on the recommendations of the Ad Hoc Committee of the American Heart Association Committee on Standards for Pediatric Cardiac Centers,[4] the improved results for the child undergoing cardiac surgery are evident in a decrease in operating time and improvement in operative and postoperative morbidity and mortality. In addition, this commitment and competency has positively influenced the remainder of the professional team.

Specific Divisions

Invasive Cardiac Diagnostic Facilities:

Cardiac catheterizations and other specific tests of an invasive nature are carried out in the Cardiovascular Diagnostic Laboratories of Northwestern Hospital, which existed before the hospital opened and were not, therefore, duplicated. The cardiovascular laboratory is connected by a direct tunnel to Children's Health Center and Hospital. Patients are also studied in the Cardiovascular Diagnostic Laboratories at Mount Sinai Medical Center, another close diagnostic facility already existent, transported by medical bus or ambulance, by certain of the pediatric cardiologists. The children are transported under specific nursing supervision to and from the catheterization laboratories. These laboratories fulfill all of the Criteria for Standards of the Intersociety Committee.[4] Infants are transported in an identical fashion as the ill premature, attended by nurses from the Neonatal Intensive Care Unit who remain throughout the procedure in the laboratory. Frequently, a member of the Department of Anesthesiology is present, particularly if the patient requires respiratory assistance. The laboratories are fully equipped for biplane fixed film angiography, cine fluorography utilizing image intensifying techniques, and microblood analyses. The entire laboratory is computerized and monitoring systems are of an elaborate nature.

The total number of procedures from the hospital's opening in February of 1973 through November 15, 1978 was 1124, an average of 225 procedures per year.

Non-Invasive Diagnostic Facilities

Electrocardiography

Over 5000 electrocardiograms have been carried out at Children's Health Center utilizing the services of a skilled and compassionate electrocardiographic technologist.

Echocardiography

Single crystal or M-mode echocardiography was established in the non-invasive diagnostic laboratories of adjacent Northwestern Hospital. In 1974-75, a technologist was selected and trained and echocardiography began on pediatric patients in the fall of 1975. The total pediatric numbers done to date are 1152. There are two highly skilled echocardiographic technologists under pediatric cardiologists' supervision carrying out these studies. The equipment is mobile, and studies are frequently done on neonates in the intensive care unit at adjacent Children's Health Center by these technologists. Since mid-summer of 1978, a two-dimensional Phased Array, 80°, sector scanner of real time type, has been in use, and 58 pediatric cases have been done. Echocardiography is an important part of the diagnostic program at Children's Health Center in Minneapolis and its activities are supervised by Dr. Amarjit Singh, one of the staff cardiologists.

Outreach Program

Such a program in preparation of patients for diagnostic studies or surgery at Children's Health Center is a valuable aid. Hospital tours are given and the children and parents are shown the beds they will be in, the diagnostic facilities they will be part of; both parents and children have benefited from such enlightenment. The Primary Nurse Concept has often resulted in followup visits in the home or by telephone before and after surgery to allay apprehension and anxiety on the part of patients and parents and relatives. Followup care also often utilizes county nursing visits as well. The patient's overall cardiovascular status is continuously monitored by the cardiologist together with the referring primary physician.

Support Group

"Parents for Heart", a support group established and functioning at Children's Health Center as its home base, has members present from all parts of the Metropolitan area and also outlying parts of the state.

Its purpose is to provide a mutual support and education program for the parents of children with cardiovascular diseases. It is sanctioned by the Minnesota Heart Association.

The Surgical Program at Children's Health Center

Cardiac surgery began at Children's Health Center in March of 1973. The summary of the surgical procedures from that time until November 15, 1978 appear in Tables 1 and 2.

Discussion and review of the cardiovascular surgical deaths:

1. Open Heart Cases: 253 cases utilizing total cardiopulmonary bypass were carried out at CHC between March 6, 1973 and November 15, 1978.

2. Closed Heart Cases: 301 closed procedures (no cardiopulmonary bypass used, however, some with pump standby) were carried out in the same time.

3. The total number of these surgical cases was 554.

A. Cases utilizing total cardiopulmonary bypass: There were 36 deaths (total number 253):

1. Ventricular septal defect:
   53 patients, 4 deaths:
      1 — age 4 months
      1 — age 8 months
      2 — age 13 months (high pressure VSDs)
2. Complete AV canal (five requiring mitral valve replacement):
   13 patients, 3 deaths:
      1 — 18 months (mitral valve replacement)
      1 — 12 months (no mitral valve replacement)
      1 — 24 months (no mitral valve replacement)
3. Total anomalous pulmonary venous connection:
   5 patients, 3 deaths:
      2 — 30 days
      1 — 6 months
4. Tetralogy of Fallot:
   A. 52 patients, 9 deaths:
      3 — 1-2 years
      2 — 2-3 years
      3 — 3-5 years
      1 — 6-12 years
   B. One patient with pulmonary atresia utilizing conduit expired at age 12 years.
5. Aortic valvotomy:
   11 patients, 3 deaths:
      2 — 30 days of age
      1 — 8 months (also had coarctation of the aorta)

TABLE 1
Open Heart Procedures
March 1973 — November 1978

SURGICAL THERAPY	8-30 Days	30 Days - 6 Months	7 Months - 12 Months	1-2 Years	2-3 Years	3-5 Years	6-12 Years	13+ Years	TOTAL
Ventricular Septal Defect		1 (1)	8 (1)	15 (2)	9	9	11		N=53
Secundum Atrial Septal Defect (some with partial anomalous pulmonary venous communication)				2	2	12	30	4	N=50
Primum Atrial Septal Defect			1	1		5	6		N=13
A-V Canal Repair									
a) Complete			2 (1)	4 (1)	1	1			N=8
b) A-V Canal with mitral valve replacement				2 (1)			3		N=5
Total Anomalous Venous Connection	1	3 (3)	1						N=5
Tetralogy of Fallot — Complete Repair		1	3	17 (3)	4 (2)	18 (3)	9 (1)		N=52
Pulmonary Valvotomy				1		2	2		N=5
Anomalous Muscle Bundles, right ventricle - infundibular obstruction						1		1	N=2
Aortic Valvotomy	2 (2)	2	1 (1)			1	3	2	N=11
Mitral Valvotomy	1 (1)								N=1
Aortic Valve Replacement	1 (1)								N=1
Mitral Valve Replacement			1					1	N=2
Combined Mitral and Aortic Valve Replacement								1	N=1
Subaortic Stenosis				1		1	1		N=3
Mustard's Operation									
a) Uncomplicated			2	3	2				N=7
b) Complicated		1 (1)	1 (1)	3	1	1 (1)	1	1	N=9
Fontan Procedure for Tricuspid Atresia							1		N=1
Atrial Septal Defect with Pulmonary Stenosis				2		1	1		N=4
Atrial Septal Defect/Ventricular Septal Defect	3		1		1		3		N=8
Right Ventricle — Pulmonary Artery Conduit					1		3 (2)		N=4
Re-op Tetrad			1		2				N=3
Removal Pulmonary Artery Band/Ventricular Septal Defect					1	2			N=3
Miscellaneous Complex Cases							1 (1)		N=1
Aortic — Left Ventricle Fistula							1		N=1
									Total: 253

N = Number
( ) = Death

6. Mitral valvotomy:
   1 patient, 1 death:
   1 — 30 days
7. Aortic valve replacement:
   1 patient, 1 death:
   1 — 30 days.
8. Mustard operation (intra-atrial baffle for redirection of venous return for treatment of d-transposition of the great arteries of the heart):
   A. Uncomplicated: 7 patients, 0 deaths.
   B. Complicated (including closure of VSD, removal of pulmonary artery band, treatment of subpulmonic stenosis):
   9 patients, 3 deaths:
   1 — 3 months
   1 — 8 months
   1 — 4 years
   C. Two Rastelli procedures were carried out for d-transpositions with VSD and pulmonary artery band:
   2 patients, 1 death: 1 — age 12 years
9. Miscellaneous complicated case: One patient with VSD, with pulmonary hypertension and severe tricuspid insufficiency, was treated by closure of the VSD and replacement of the tricuspid valve, but the patient expired, at age 7 years.
   B. Closed Procedures: 12 deaths (Total Number 301)
10. Blalock-Hanlon Procedure: Excision of a portion of the atrial septum utilizing pulmonary venous inflow occlusion (to increase mixing, in treatment of d-transposition of the great artery cases):
    18 patients, 3 deaths:
    2 — less than 1 month
    1 — less than 3 months
    (These deaths occurred early in our experience)
11. Waterston Procedure: Ascending aorta to pulmonary artery shunt, direct connection (to increase pulmonary blood flow):
    13 patients, 2 deaths:
    1 — 3 days
    1 — 1 month
12. Potts Procedure: Descending aorta to left pulmonary artery direct anastomosis:
    3 cases, 1 death:
    1 — 8 days
13. Patent Ductus Arteriosus:
    A. Division of patent ductus under the age of 30 days: 2 deaths, both associated with marked friability of the ductus and bleeding.
    B. One death occurred at age one month.
    C. Total number of cases operated upon was 139 ranging in age from 3 days to 13 years, with the vast majority occurring in the infant age group.
14. Coarctation of the Thoracic Aorta:
    56 patients, 2 deaths:
    1 — first week of life (associated with marked tubular hypoplasia of the arch and VSD)
    1 — first month
    3 unusual cases were encountered:
    A. A dacron conduit utilized between the ascending and descending aorta for complex coarctation involving the left carotid artery with left subclavian steal syndrome.
    B. An intraluminal shunt placed within an unusual coarctation in the mid-thoracic aorta.
    C. An angioplasty for recurrence of coarctation with an onlay graft.
    D. Three infant coarctation patients underwent pulmonary artery banding at the same time as coarctation resection, to control massive pulmonary blood flow and pulmonary hypertension from intracardiac shunts, all survived.

TABLE 2

Closed Heart Procedures
March 1973 — November 1978

SURGICAL THERAPY	AGE	0-7 Days	8-30 Days	30 Days - 6 Months	7 Months - 12 Months	1-2 Years	2-3 Years	3-5 Years	6-12 Years	13+ Years	TOTAL
Blalock-Hanlon Procedure		6 (2)	3	8 (1)							N=18
Blalock-Taussig Anastomosis				7	3	3	1	3	1	2	N=20
Waterston's Procedure (Ascending Aorta-Pulmonary Artery)		5 (1)	4	2 (1)		1		1			N=13
Potts Procedure (Descending Aorta — Left Pulmonary Artery)		1 (1)					2				N=3
Synthetic Graft (Aorta — Pulmonary Artery Shunt)		4	1	5	1	1	1		1		N=14
Patent Ductus Arteriosus		18 (2)	36	18 (1)	19	14	4	12	12	1	N=139
Coarctation		1	7 (1)	8	4	4	1	10	16	5	N=56
Pulmonary Artery Banding			1 (1)	10 (2)	3	1					N=15
Pulmonary Valvotomy with Inflow Occlusion		5 (1)		5	1	1	2	3	1	2	N=20
Closure of Aorto-Pulmonary Shunt								1			N=1
Interruption of Aorta				2 (1)							N=2
Permanent Implanted Pacemaker for Heart Block*											Total: N=301
a) Congenital or Medical					1				1	1	N=3
b) Surgically Acquired					1	4	1		4	1	N=11
Pacemaker Generator Replacement						1	4	2	4	1	N=12
											Total: 327

---

*Eight of eleven primary implants for surgically induced heart block had their original surgery here.

N = Number
( ) = Death

15. Pulmonary Valvotomy Utilizing Inflow Occlusion:
    20 patients, 1 death: 1 — within the first week.
16. Interruption of Aortic Arch:
    2 patients, 1 death.

Such a committed program has other objectives which include making provisions for the training of surgical and pediatric residents; continuing case review; review of new techniques, scientific inquiry into new ideas. Meticulous conferencing is mandatory and has been carried out in a formal fashion at working cardiovascular conferences prior to any invasive diagnostic studies and after for their discussion in the preparation for surgery. The team interaction is essential and employs all of its aspects to the fullest.

The cardiovascular team at Children's Health Center, Minneapolis, has been self-critical and will continue to be so. If further changes are needed, this will occur through the team which will implement such changes always with the best care of the child being the ultimate factor. Because of the team's dedication, self-criticism and evaluation, abilities, and the desire to give ever better care for children, the entire staff of the cardiovascular team at Children's Health Center in Minneapolis look forward to a continuing improving program.

Summary

The pediatric cardiology program at Children's Health Center, Minneapolis, is a well-established, continuously improving system of interdisciplinary approach. It has demonstrated over time that it has strength and commitment, and represents an important part of the philosophy of Children's Health Center, from its dreams in the minds of men and women of this city of 30 years ago to the present — "the best possible care for children".

Acknowledgment

The author is grateful for the technical assistance of Sandra Abraham, RN, Department of Surgery, Children's Health Center.

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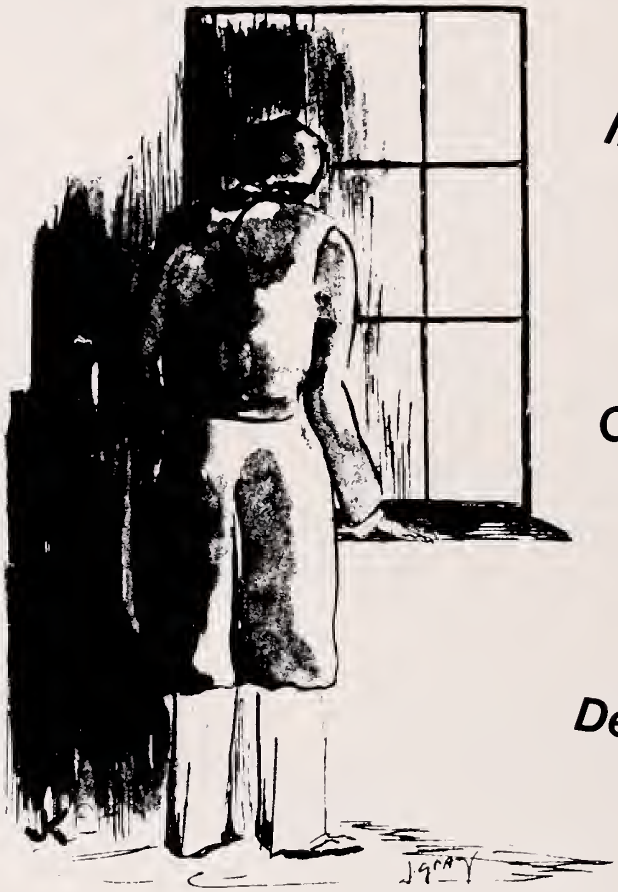
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Meconium Aspiration Syndrome

Treatment of the Clinical Problem

DAVID B. KLAIN, M.D.* and G. ERIC KNOX, M.D.†

The problems of meconium aspiration syndrome are best treated in a preventative manner. The presence of meconium in the antepartum or intrapartum period is not necessarily indicative of fetal distress. Aggressive management including close monitoring and airway toilette are recommended as means of eliminating the perinatal mortality.

MECONIUM ASPIRATION syndrome is one of the most difficult problems faced by physicians involved in perinatal care. The reported incidence of meconium stained amniotic fluid varies considerably ranging from 8%[1] to 29%[2] with the variation probably accounted for by the type of nursery (referral or general) reporting. Likewise, the severity of the meconium aspiration syndrome varies considerably from one report to another. In established cases, the mortality ranges between 0%[3] and 28%[4]. Recent clinical studies have suggested that in the presence of meconium, aggressive perinatal management of mothers, fetuses, and neonates can prevent almost all mortality and morbidity.[1,3] The purpose of this report is to suggest guidelines for the management of a pregnancy in which meconium is present, based on principles established by an understanding of the disease pathogenesis.

Obstetrical Considerations

Pregnancies complicated by the presence of meconium have a higher perinatal mortality than those in which the amniotic fluid remains clear.[5] This observation, together with the demonstration of low oxygen saturation (15% to 25%) in umbilical vein blood following meconium passage,[6] led to the empiric practice of using the antenatal discovery of meconium via amnioscopy or amniocentesis as a sign of intrauterine compromise.

More recently, the use of meconium as a specific and sensitive antenatal monitor of fetal distress has been seriously questioned. In the large series of patients reported by Saling,[7] only 1.7% of fetuses were acidotic at the time meconium was detected during antenatal assessment. More recently, Paul et al.[8] demonstrated that fetal death could occur in the absence of meconium passage, while in a retrospective study, Huddleston[9] could not find an association between a positive oxytocin challenge test and the presence of meconium. Knox et al.[10] in a prospective study of prolonged pregnancies concluded that the use of meconium as an indicator of fetal distress did not lead to a reduction in perinatal mortality, and that a search for meconium in this clinical situation was not warranted. Similar conclusions were reached by Miller et al.[2] in an intrapartum (rather than antepartum) study concerning the significance of meconium. These authors concluded that intrapartum meconium in the absence of concurrent fetal heart rate or acid-base abnormalities does not indicate fetal compromise. It was suggested that with appropriate airway management of the infant at the time of birth and in the absence of biochemical or biophysical evidence of hypoxia or asphyxia, meconium is of little significance.

If not an indicator in intrauterine compromise, why then is meconium associated with suboptimal perinatal outcome, and what can the attending physician do to prevent the increase in perinatal mortality found with it? It is not unreasonable to suggest that the poor perinatal outcome associated with meconium may in fact be related to events occurring during labor and delivery which are totally unrelated to intrauterine fetal distress. Examples which come readily to mind include induction of labor with resultant iatrogenic hypoxia[11], cesarean section[12], or meconium aspiration[1,13]. As detailed below, neonatal aspiration of meconium is probably the most prevalent and awesome of these possibilities.

Pathogenesis of the Aspiration Syndrome

An adequate understanding of the pathogenesis of the meconium aspiration syndrome is necessary in order to intervene at the proper times and in an effective manner. The usual infant with meconium aspiration syndrome is at or near term, the vast majority being greater than 37 weeks gestation. Many of the patients experiencing this problem are post dates with approximately 30% being greater than 42 weeks gestation.[2] The second component which appears to be necessary is fetal asphyxia. The presence of these previously mentioned factors, i.e. a relatively mature infant plus hypoxia, added to the presence of meconium in the amniotic fluid leads to the problems the infant faces at delivery.

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As the fetus is stressed with hypoxemia, he attempts to gasp, bringing the meconium into the trachea, resulting in the greatest concentration of meconium occurring proximal and lesser amounts distal in the trachea itself. Then, with the onset of breathing, the meconium is moved along the airways to the small bronchioles where significant obstruction takes place. Secondary infiltrate with PMNs is noted and the patient experiences shunting, air trapping, and great risk of pneumothorax. This appears in approximately 20% of all patients.[14] Figure 1 explains the reason for air trapping and pneumothorax with the presence of meconium.

Antepartum and Intrapartum Management

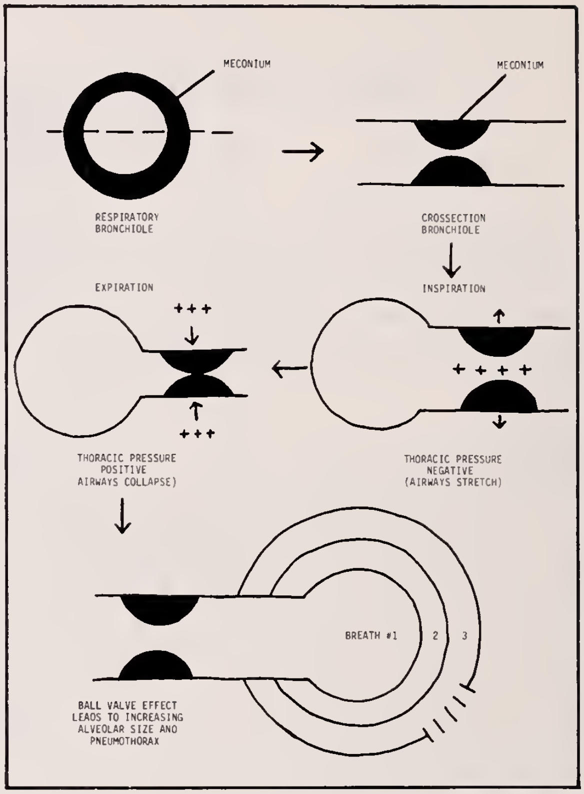
Optimal antenatal and intrapartum care for the patient with meconium while no different from optimal care of any other high risk gravida should include the following:

1. Antenatal assessment of uteroplacental function through biophysical or biochemical means (e.g. oxytocin challenge testing, serum estriols, etc).
2. Judicious timing of delivery based on the results of fetal placental assessment, maternal condition, and fetal maturity.
3. Intrapartum prevention of hypoxia and acidosis through the use of continuous electronic fetal heart rate monitoring and determination of scalp pH.

Adherence to these principles should lead to improvement in the care of pregnancies that are complicated by the presence of meconium in the amniotic fluid.

There have been several studies published which have demonstrated that the best treatment for infants who were born with thick meconium stained amniotic fluid is implemented in the delivery room.[1,13] The first therapy which one should initiate when finding meconium stained fluid is as follows:[3]

1. At the time of delivery of the head, good cleaning of the nasopharynx should take place. First the mouth, then the nose. This can be done with DeLee suction or with a suction bulb.[13]
2. After delivery, the child should be kept in a Trendelenburg position in order to encourage drainage of the meconium down into the nasopharynx.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MECONIUM
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CROSSECTION BRONCHIOLE
EXPIRATION
+++
+++
INSPIRATION
++++
THORACIC PRESSURE POSITIVE AIRWAYS COLLAPSE)
THORACIC PRESSURE NEGATIVE (AIRWAYS STRETCH)
BREATH #1
2
3
BALL VALVE EFFECT LEADS TO INCREASING ALVEOLAR SIZE AND PNEUMOTHORAX

Figure 1

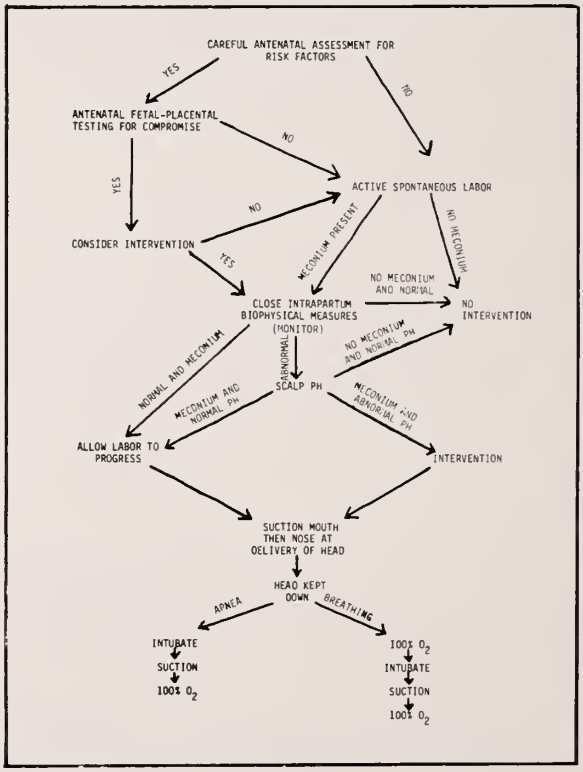
CAREFUL ANTENATAL ASSESSMENT FOR RISK FACTORS
YES
NO
ANTENATAL FETAL-PLACENTAL TESTING FOR COMPROMISE
NO
YES
ACTIVE SPONTANEOUS LABOR
NO
CONSIDER INTERVENTION
YES
MECONIUM PRESENT
NO MECONIUM
NO MECONIUM AND NORMAL
CLOSE INTRAPARTUM BIOPHYSICAL MEASURES (MONITOR)
NO INTERVENTION
NORMAL AND MECONIUM
ABNORMAL
NO MECONIUM AND NORMAL PH
SCALP PH
MECONIUM AND NORMAL PH
MECONIUM AND ABNORMAL PH
ALLOW LABOR TO PROGRESS
INTERVENTION
SUCTION MOUTH THEN NOSE AT DELIVERY OF HEAD
HEAD KEPT DOWN
APNEA
BREATHING
INTUBATE
SUCTION
100% O2
100% O2
INTUBATE
SUCTION
100% O2

Figure 2

3. Upon placing the infant in a warm environment, the infant's head should be turned from side to side, and as much meconium as possible collected in the bucal area and suctioned out.
4. If the infant is apneic, immediate deep tracheal suctioning should be performed either with large bore catheter (10 or 12 French suction catheter) or through an endotracheal tube and then oxygen administered.
5. If the infant is having some breathing motion, 100% oxygen should be delivered, then deep tracheal suctioning undertaken as in 4.

One must be aware that the basic factors which cause meconium aspiration are a combination of meconium plus asphyxia. The treatment mentioned previously deals mainly with meconium with little attention towards asphyxia. One must keep in mind during the entire procedure that the infant may be hypoxic and acidotic, and that care must be taken to proceed as rapidly as possible in order to gain adequate oxygenation as soon as possible.

Some recommendations have been made with regards to not suctioning the trachea if meconium is not visible on the vocal cords. It is our feeling that the patient who is delivered through thick meconium stained amniotic fluid with evidence of hypoxia should have tracheal suctioning even if no meconium is visualized on the cords.

The previously described method of treatment for meconium aspiration syndrome in the delivery room has been proven by statistical methods and practice to be of advantage and help to infants.

There are several other therapies which are often undertaken which may or may not have therapeutic efficacy. The first of these which has been mentioned in many cases is steroids.[15] Although in previous discussion it was stated that meconium, as it reaches the terminal bronchiole, enters the lung tissue causing inflammatory reaction with PMNs, at the present time, there is no proof that the anti-inflammatory effect of steroids in any dosage regimen is of any advantage in meconium aspiration syndrome. Another mode of therapy which has been recommended is antibiotics. The thought behind antibiotics is that even though meconium is a sterile fluid, secretions pool behind meconium plugs in the lungs causing a secondary infection. There is also no evidence that this is of great benefit to infants with meconium aspiration syndrome. Because meconium has a thick, tenacious nature, tracheal lavage has been recommended.[16] At the present time there is no clear evidence that this would be of benefit to the infant.

Once adequate tracheal suctioning has been undertaken and as much meconium as possible retrieved from the trachea, the infant is then taken to the nursery for close observation. Because of the dynamics of the illness with meconium passing slowly towards the terminal bronchioles, it may take as long as 48 hours before significant symptoms of meconium aspiration syndrome arise and close observation for at least that period of time is warranted. Also during this 48 hour period two other phenomena may be noted. Both of these are probably secondary to the asphyxia which the infants may have suffered during the immediate prepartum and postpartum periods. These complications are seizures and inappropriate secretion of antidiuretic hormone.[17]

Once the lung disease becomes established, the only treatment is supportive. At times it has appeared to be helpful to treat these children with low level distending pressure and on occasion, intravenous Priscoline. Vigorous chest physiotherapy including percussion, vibration, suctioning, and positioning, along with humidified oxygen is thought to be helpful. Very often in severe symptomatic cases the illness is progressive and unrelenting with the patient ultimately expiring.

In those infants which survive meconium aspiration syndrome the clinician should be aware of the fact that asphyxia played a role in the establishment of the meconium aspiration within the lungs. Although the pulmonary disease may resolve, the long term effects of asphyxia cannot be determined. It is therefore quite important to follow these infants long term for evidence of developmental delay with institution of proper corrective therapy if possible.

Summary

The phenomena of meconium stained amniotic fluid is common with incidences between one in 12 and one in 4 deliveries. The key to treatment of the meconium aspiration syndrome is aggressive perinatal management and immediate intervention at the time of birth. Once the illness becomes established it is one of the most difficult illnesses to treat. Immediate intervention in the delivery room can save lives and improve quality of survival for many patients. It is our feeling, therefore, that all professionals engaged in care of mothers and babies should be very aware of the proper approach to this problem.

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4.-17. Will be found on page 466.

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CONTRAINDICATIONS: Advanced arteriosclerosis, hyperthyroidism, known hypersensitivity, or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors, (hypertensive crises may result).

WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence:* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy:* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children:* Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System:* Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic:* Urticaria, rash, ecchymosis, erythema. *Endocrine:* Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System:* Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous:* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.

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Lateral Decubitus Radiograph of the Chest in Pediatric Radiology

An Additional Use

LELAND H. PREWITT, JR., M.D.* and SHASHIKANT M. SANE, M.D.*

Interpretation of chest radiographs in children with possible pneumonia is frequently made difficult by prominent bronchovascular markings in the medial aspects of the lung which simulate pneumonia. The lateral decubitus film of the chest is often helpful in distinguishing prominence of normal lung markings from consolidative penumonia or atelectasis. Our experience with this technique and the physiologic basis for its usefulness are described in this report.

THE LATERAL DECUBITUS radiograph of the chest has been traditionally used to detect pleural effusion. Other uses of this technique have included detection of obstructive emphysema and confirmation of pneumothorax. A recent publication in November 1977 emphasizes the use of this technique in children with possible pneumonia.[3] During the past 24 months we too have found the lateral decubitus film of great help in evaluating children whose frontal and lateral radiographs of the chest have shown equivocal changes of consolidation or atelectasis. The purpose of this paper is to illustrate and discuss this method of evaluation, emphasizing the physiologic principles that underlie its usefulness.

Materials and Methods

During the last 24 months the lateral decubitus technique was used to evaluate "possible pneumonia" in 37 children. Twenty-five of these 37 children were referred for pre-operative chest examinations. The remaining 12 were referred to rule out pneumonia. The lateral decubitus film was obtained only when the frontal radiograph of the chest was suggestive of pneumonia, and the lateral was either normal or equivocal. If a pneumonic process was definitely present on either the frontal or lateral film, a lateral decubitus film was not obtained.

In obtaining the lateral decubitus film the child is positioned with the side down opposite to the area in question. A foam rubber pad four inches thick is placed underneath the child. Towels are placed under the head to prevent bending of the cervical and upper thoracic spine. In infants and small children the arms are placed

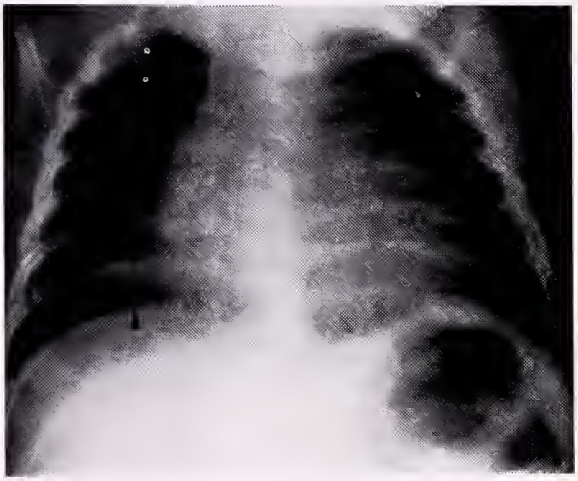

Fig. 1(A) — The preoperative frontal film reveals a confluent area of water density at the right cardiophrenic angle. The lateral view was normal.

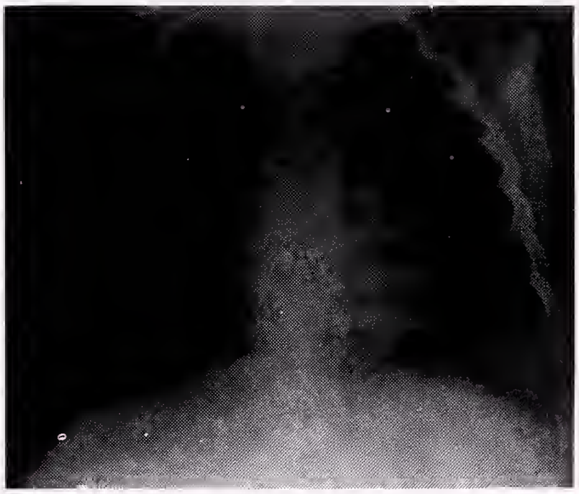

Fig. 1(B) — The left lateral decubitus film produces hyperinflation of the right lung which separates the bronchovascular markings. The medial aspect of the right lower lobe is normal. The apparent pneumonia is due to confluence of bronchovascular markings.

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*Department of Radiology, Minneapolis Children's Health Center, Minneapolis, Minnesota.

in a stockinette to prevent movement during the exposure. Younger children are held at both the head and feet to prevent rotation which might obscure the area in question. Whenever possible, the parents are given lead aprons and gloves and asked to assist in holding the child to prevent radiation exposure to the technologists. A simple casette holder is employed to hold the film. A horizontal beam is then used for the exposure. The decubitus film is viewed as if it were an upright film to enhance comparison with the standard frontal view.

Results

In 17 cases the decubitus film was obtained to exclude parenchymal disease in the medial portion of the right lower lobe (right cardiophrenic angle). In 11 cases the questionable area was the right middle lobe. Of the remaining nine cases the areas in question were either in the lower portion of the left lung or both lower lobes.

Based on the lateral decubitus film, the radiographic examination was interpreted to be normal in 27 of 37 cases. Six of the ten abnormal cases had disease in the right middle lobe, two in the lingula and two children had pneumonic changes in both lower lobes.

Discussion

A frequent indication for the radiographic examina-

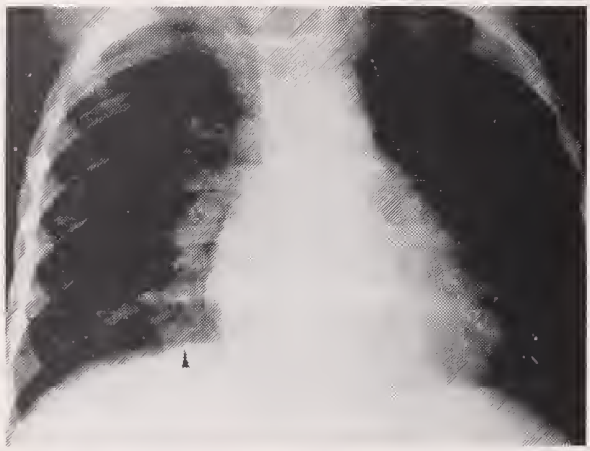

Fig. 2(A) — A preoperative film reveals confluent water density at the right cardiophrenic angle. The lateral view was normal.

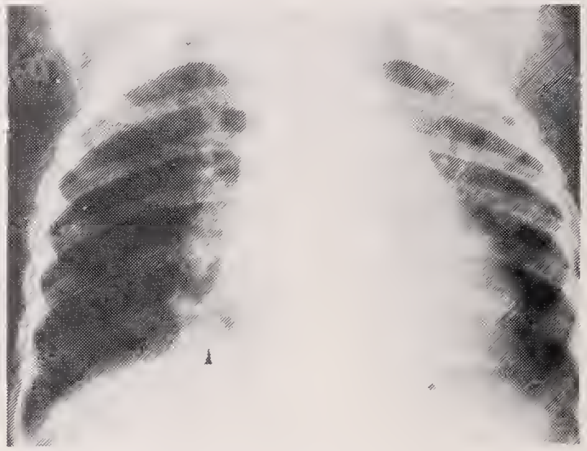

Fig. 2(B) — A left lateral decubitus view of the chest demonstrates hyperinflation of the right lung. Despite this hyperexpansion the confluent water density persists confirming the presence of consolidation in the medial segment of the right lower lobe.

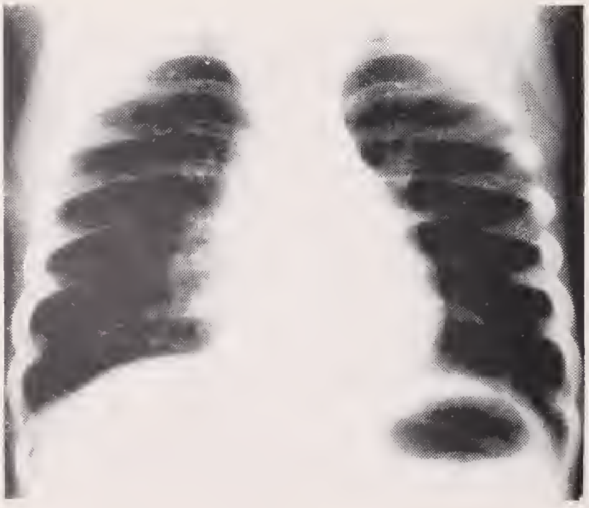

Fig. 3(A) — Ill definition of the right heart border is seen on the frontal view of the chest. The lateral view was equivocal. This usually indicates disease in the right middle lobe but not invaribly.

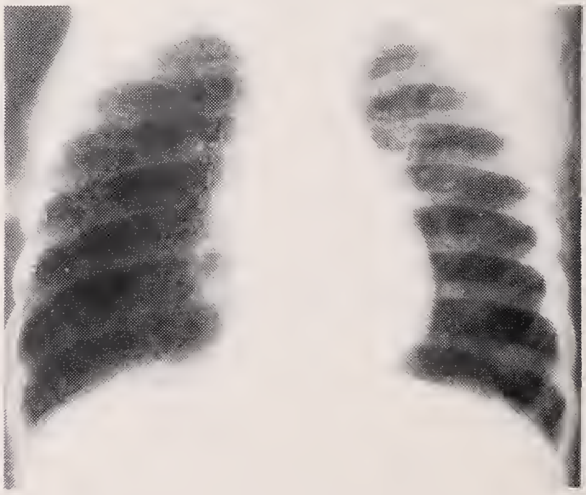

Fig. 3(B) — The left lateral decubitus position has produced hyperinflation of the right lung separating the bronchovascular markings. The right border of the heart is now distinct indicating that the ill definition seen on the upright view is due to crowding of normal markings.

tion of the chest in infants and children is "possible pneumonia". The exclusion of this diagnosis may be difficult even for the experienced observer. Not infrequently the frontal radiograph of the chest will reveal areas of water density adjacent to the heart borders, at the cardiophrenic angles, or in the retrocardiac area. A lateral view may be normal if the area of water density is small or superimposed on the cardiac shadow. A dilemma arises as to whether the areas seen on the frontal view represent confluence of normal bronchovascular markings or pneumonia. Oblique views may be helpful but often are positioned inappropriately to be of value. Repeating the examination or changing the position of the child for the frontal film from upright to recumbent, or vice versa, may also be helpful. However, these techniques are not consistently beneficial. We have found that a lateral decubitus view with the side down opposite to the area in question has consistently been valuable in distinguishing normal from abnormal.

The lateral decubitus technique will selectively hyperinflate the higher lung containing the possible pneumonia. The pulmonary vessels will be separated by this hyperexpansion and no longer appear confluent. In addition, the pulmonary blood flow will be decreased in the superior lung, thus diminishing the size of the pulmonary vessels.[3] These changes enable differentiation between prominent vascular markings and focal consolidation and/or atelectasis which will persist as confluent water density despite the hyperinflation and decreased perfusion. Our data indicate that the areas of the lung where this procedure has been most helpful are the medial portion of the right lower lobe and right middle lobe. It is these areas that most frequently create problems in interpretation. This is probably due to the right hemidiaphragm being slightly higher than the left on upright films which results in asymmetrical crowding of bronchovascular markings. In addition, the absence of the cardiac shadow on the right side allows the vascular markings in the right infrahilar area to appear more prominent than those on the left.

Our explanation for the observed differences in regional ventilation in the decubitus position differs from that offered by Kaufman, et al.[3] They maintain that the dependent hemithorax is trapped by virtue of its position. The higher lung which is not restricted is thus thought to be compensatorily hyperinflated. This is inaccurate. While the higher lung does indeed contain a greater volume of air, the lower lung instead of being trapped receives a relatively greater amount of air with each ventilation. We have confirmed this by examining children fluoroscopically in the lateral decubitus position. The dependent hemidiaphragm has greater excursion than the superior hemidiaphragm. This indicates greater movement of air in the lower lung and demonstrates that it is not trapped by virtue of its position.

Differential aeration of the two lungs in the lateral decubitus position is due primarily to the effect that gravity has on ventilation.[2] Experimentally it has been shown that differences in the regional distribution of inspired air are due to differences in the static transpulmonary pressure that exist in various regions of the lung.[4] Intrapleural (transpulmonary) pressure is

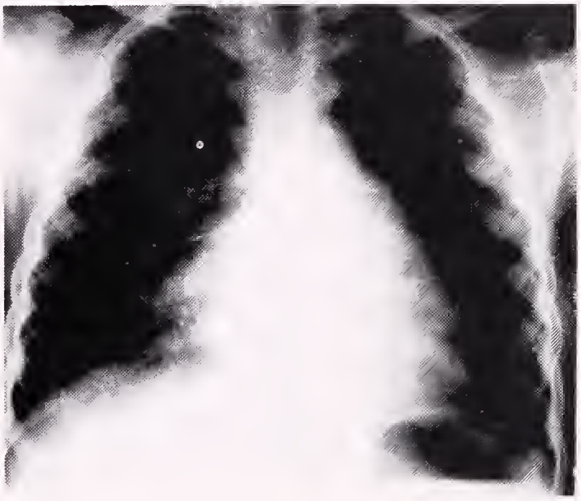
Fig. 4(A) — Ill definition of the right border of the heart is seen on the frontal view in this child. The lateral view was equivocal.

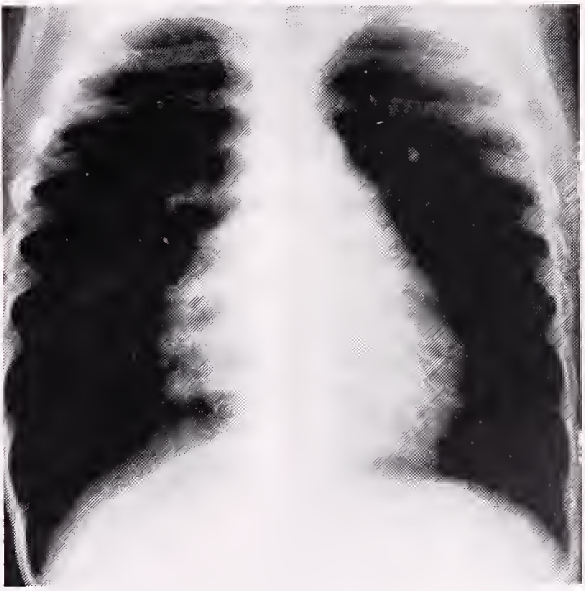
Fig. 4(B) — Despite the hyperinflation produced by the left lateral decubitus position the ill definition of the right border of the heart persists confirming focal disease in the medial segment of the right middle lobe.

normally sub-atmospheric.[2] This pressure is not uniform throughout the pleural space but is more negative in the higher zones of the lungs and increases towards the lower zones (becomes less negative).[2] Therefore, a gradient of pleural pressure exists which is about 0.20 cm. of water per cm. of vertical height.[2] The complete explanation for this gradient is not fully understood, but is probably related to the weight of the thoracic contents.[6] It is certainly gravity dependent since reversal of body position reverses the gradient.[4] The effect of this gradient is two-fold. Firstly, the acini in the upper zones of the lung where the pleural pressure is more negative will be more expanded than those in the lower zones at any lung volume except total lung capacity. Secondly, the lower zones will receive more regional ventilation with each inspiration. An exponential relationship exists between the volume of the lung and the pleural pressure. As a result of less sub-atmospheric pressure in the lower zones of the lung because of the gradient, these regions lie on a steeper part of the volume/pressure curve than the higher zones. Therefore a given change in pressure will produce a greater change in volume in the lower regions of the lung than the upper regions.[4]

Pulmonary perfusion of blood is likewise affected by gravity. The lower areas of lung receive more flow than the higher areas. Thus, the vessels in the higher areas will be smaller in caliber than those in the lower areas.[2]

Additional useful information can be obtained from the lateral decubitus technique. A small pleural effusion can be detected that is not otherwise seen. If pulmonary consolidation is evident, presence of fluid in the pleural space suggests a bacterial rather than a viral etiology for the pneumonia.[5] Obstructive emphysema in the dependent lung may incidentally be discovered. The presence of a non-radiopaque foreign body in the trachea is sometimes evident on the standard frontal and lateral views. However, if the foreign body is lodged in the intermediate bronchus, air trapping may not be apparent on the standard views. The lateral decubitus film may demonstrate this air trapping in the dependent lung, suggesting the presence of a foreign body which may have been aspirated without the awareness of the parents.[1] Finally, a small pneumothorax in the superior lung may be made evident by the lateral decubitus radiograph. This is a possibility in a child with an acute asthmatic attack who, in addition to experiencing respiratory distress, is complaining of chest pain.

Summary

1. The lateral decubitus view is a simple and useful means of evaluating the infant or child with a "possible pneumonia" when frontal and lateral views of the chest show equivocal changes. Additional information which may alter the diagnostic and therapeutic approach to the patient may also be obtained from the decubitus film.

2. The physiologic basis for the usefulness of this technique has been briefly reviewed. Due to differences in pleural pressure, the higher lung is hyperinflated relative to the lower lung. This combined with diminished perfusion of the higher lung separates normal pulmonary vessels enabling differentiation between confluent vascular shadows and penumonia.

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The Use of 1-desamino-8-D-arginine Vasopressin (DDAVP) in the Management of Neurogenic Diabetes Insipidus

(Multiple Etiologies in Pediatric Patients)

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Neurogenic diabetes insipidus is a syndrome characterized by polyuria and polydipsia secondary to a deficiency of antidiuretic hormone. DDAVP is a therapeutic agent which has recently been introduced for the treatment of diabetes insipidus. DDAVP has many advantages over previously employed treatments (aqueous vasopressin, vasopressin tannate in oil, lysine vasopressin) in that it has specific antidiuretic hormone activity, a prolonged duration of action and minimal side effects. Presented is clinical experience with the first six patients treated with DDAVP at Minneapolis Children's Health Center. The data suggests that DDAVP should be the drug of choice for diabetes insipidus in the pediatric patient.

CENTRAL NEUROGENIC DIABETES insipidus (DI) is a disorder of multiple and diverse etiologies. The management of this condition has been among the most difficult and primative encountered in contemporary endocrinology. Problems have included the limited availability of impure, obligatorily injectable, inconvenient therapeutic agents of variable degree and duration of antidiuretic activity, and many associated side effects. These problems are compounded in the pediatric patient.

The management of the child with DI requires a highly purified, potent, and therapeutically consistent agent, which has specific antidiuretic hormone (ADH) activity. This agent should have a reasonable duration of action, minimal toxicity and pressor effects, and be administered by a noninjectable route.

1-Desamino 8-D-arginine vasopressin (DDAVP) appears to meet these criteria and may provide better clinical and chemical control than previous clinically available substances. DDAVP has unique and important advantages in the management of central DI, regardless of etiology, as demonstrated in our pediatric patients.

Materials and Methods

Six patients (one male, five females; ages 4 months to 14 years) with DI of multiple etiologies were admitted to Minneapolis Children's Health Center for diagnostic evaluation and initiation of DDAVP therapy (Table 1).

Patient #1 was a four-month-old male infant who developed a metabolic encephalopathy probably of a cerebral leukodystrophic variety. DI developed as a

TABLE 1

Summary of Clinical Information at Time of Evaluation

Patient #	Age	Sex	Weight (kg)	Dx	Duration of D.I.	Previous Tx
1.	4 mo.	M	7.3	neonatal metabolic encephalopathy	4 mo.	Aqueous Pitressin
2.	2 yrs.	F	8.3	head trauma	1.8 yrs.	Pitressin in Oil
3.	8 yrs.	F	25	idiopathic	6.5 yrs.	Pitressin in Oil
4.	13 yrs.	F	52	histiocytosis X	5.5 yrs.	Pitressin in Oil
5.	8 yrs.	F	25	hypothalamic germinoma	3 mo.	Regulation of fluid intake
6.	14 yrs.	F	44	head trauma	1 mo.	Chlorpropamide Regulation of fluid intake

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manifestation of his diffuse CNS disease and was initially treated with aqueous pitressin. The pressor activity of this agent produced significant cardiorespiratory distress and DDAVP was substituted with effective control of his DI.

Patient #2 developed DI following head trauma with bilateral subdural hematomas, as a result of multiple episodes of physical abuse. Initial management with pitressin tannate in oil was complicated by prolonged oliguria with associated electrolyte imbalances and recurrent seizures. DDAVP has provided optimal control with normalization of her fluid and electrolyte status and absence of overt seizures.

Patient #3 developed idiopathic DI at eight years of age. She presented with unexplained profound polyuria and polydipsia which was well controlled with pitressin tannate in oil for two years. Detailed neuroendocrine, ophthalmologic and radiographic evaluations have revealed no definable hypothalamic or pituitary disease. DDAVP was begun for convenience of administration and more control of her DI.

Patient #4 is a 13-year-old female with a five year history of histiocytosis X characterized by growth hormone deficiency and complete DI. Management with pitressin in oil was suboptimal due to painful injections, noncompliance, unpredictable electrolyte abnormalities and fluid retention with marked edema and oilguria. DDAVP provided markedly improved physiologic regulation of her DI and desirable personality changes.

Patient #5 is an eight-year-old female who developed DI following irradiation of a hypothalamic germinoma. Management of her DI was initiated with DDAVP which provided optimal control. Growth hormone deficiency and abnormalities of TSH and prolactin followed surgical excision of residual tumor. Postoperative modifications in her DDAVP continue to provide excellent clinical control of her DI.

Patient #6 is a 14-year-old female who developed a partial syndrome of DI following severe head trauma in an automobile accident. Her DI has persisted for 18 months following this injury. She was begun initially on chlorpropamide without adequate control of her DI, manifested by persistant polydipsia and frequent nocturia. Initiation of DDAVP resulted in prompt resolution of her symptoms and optimal fluid and electrolyte balance. She is without neurologic sequelae and no structural abnormalities or anterior pituitary dysfunction have been demonstrated.

DI was diagnosed by a standardized water deprivation test in all patients. Multiple low quantitative ADH levels by radioimmunoassay confirmed the diagnosis in four patients. All patients received neuroendocrine evaluation for assessment of anterior pituitary function which included serum T_4 and thyroid stimulating hormone (TSH), cortisol and adrenocorticotropic hormone (ACTH), thyrotropin releasing hormone (TRH) stimulation test for thyroid stimulating hormone and prolactin, and L-dopa and arginine stimulation for growth hormone (Table 2). Additional evaluation included skull Xrays, tomograms of the sella turcica and visual field examinations where possible.

Previous therapeutic regimens were discontinued and the patients were allowed to reach baseline control status as defined by a urine specific gravity ≤1.005 or urine osmolality <250mOsm/kg. Laboratory data including serum osmolality, sodium, potassium, complete blood count, total protein, SGOT and alkaline phosphatase were obtained prior to DDAVP therapy and at a follow-up clinic visit.

Therapy was then initiated at 2.5mcg per day and was individualized by monitoring urine specific

TABLE 2

Anterior Pituitary Evaluation

Patient	Growth Hormone (a)	TSH (b)	Prolactin (b)	ACTH (c)
#1	(+/−)	(+)	(+/−)	(+)
#2	(−)	(+)	(NT)	(+)
#3	(+)	(+)	(+)	(+)
#4	(−)	(+/−)	(+)	(+)
#5	(−)	(+/−)	(+/−)	(−)
#6	(+)	(+)	(+)	(+)

Code: (+) = Intact
(−) = Deficiency
(+/−) = Significant functional abnormality, but some residual hormone present
(NT) = Not tested to date

(a) = By L-dopa and arginine provocative release
(b) = By IV TRH (thyrotropin releasing hormone) provocative release and serum T_4 by radioimmunoassay
(c) = By serum cortisol and serum ACTH by radioimmunoassay (AM and PM) and/or metyrapone test

gravity and urine osmolality. DDAVP was administered intranasally by a plastic (rhinyle) catheter which is graded for 0.05ml (5mcg), 0.1ml (10mcg) and 0.2ml (20mcg).

Results

Fluid intake and urine output were determined for 24 hours prior to and 24 hours after the initial dose of DDAVP (Figure 1). Fluid intake and urine output decrease after DDAVP with exceptions in the younger and smaller patients. This discrepancy may be due to difficulties in assessing fluid intake and measuring urine output in such patients.

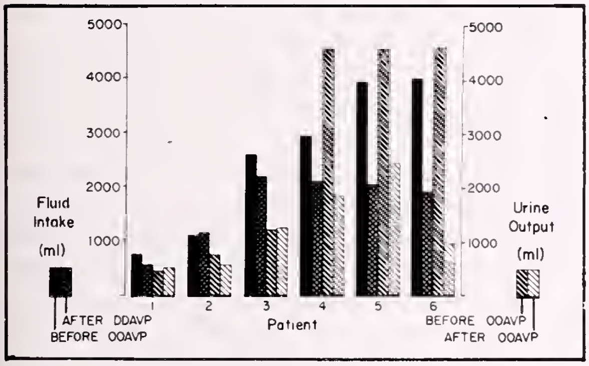

Fig. 1 — Fluid intake and urine output 24 hours prior to and after initial DDAVP dose (2.5mcg).

More dramatic changes are seen in urinary solute concentration following DDAVP administration (Figure 2). These are demonstrated by urine specific gravity and urine osmolality prior to and on the first void after DDAVP. A significant effect of DDAVP on urine concentrating ability was measured in all patients, suggesting that urinary concentrating ability is a more specific indicator of antidiuretic activity than either fluid intake or urine output volume measurements.

Serum osmolality and serum sodium were determined before and four hours after DDAVP administration (Figure 3). Serum sodium and osmolality, which were slightly elevated prior to DDAVP administration, return in almost all cases to the appropriate values. Changes in serum sodium, as seen in patient 5 following DDAVP, probably represent superimposed abnormalities such as a damaged hypothalamic thirst center. Such changes in serum data after DDAVP administration suggest that urinary concentrating ability may be more accurate to monitor DDAVP therapy.

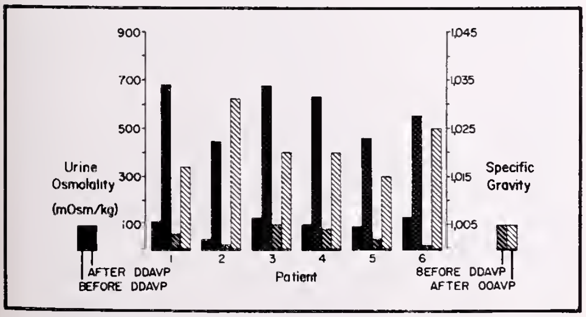

Fig. 2 — Urine osmolality and specific gravity prior to and on first void after initial DDAVP dose (2.5mcg).

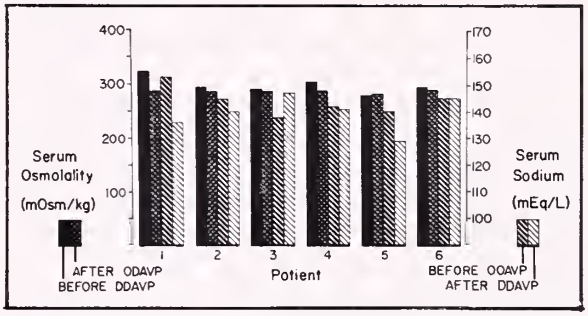

Fig. 3 — Serum osmolality and serum sodium prior to and four hours after initial DDAVP dose (2.5mcg).

Figure 4 demonstrates the response to DDAVP therapy in patient 5. Urinary solute concentration responds rapidly and significantly with each insufflation of DDAVP. With diminution of DDAVP antidiuretic effect, urine concentrating ability decreases and corresponding measurable increases in fluid intake and urine output occur.

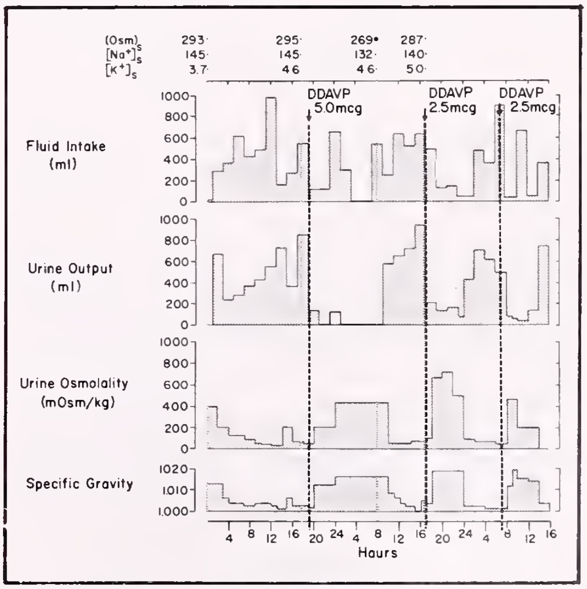

Fig. 4 — Patient #5 — DI secondary to a hypothalamic germinoma. Three day sequential monitoring of fluid balance and urinary concentrating ability.

Figure 5 illustrates patient 6 who was initially treated with chlorpropamide and unrestricted fluid intake. She was then deprived of water for 12 hours and DDAVP therapy was initiated. Urine concentrating ability rose dramatically upon institution of DDAVP. This is in contrast to only minimal changes in urinary concentrating ability with chlorpropamide therapy and water deprivation. Urinary concentrating ability is maintained and facilitated with each subsequent insufflation of DDAVP with corresponding decreases in fluid intake and urine output. Marked polydipsia and polyuria were seen with chlorpropamide therapy alone. Urinary concentrating ability rather than fluid intake and urine output volume changes represent the dramatic and specific antidiuretic effect of DDAVP. With continued fluid intake after the initial DDAVP dose, serum sodium and osmolality decreases to the lower limits of normal. Initial urine osmolality and specific gravity reflect a previous DDAVP dose.

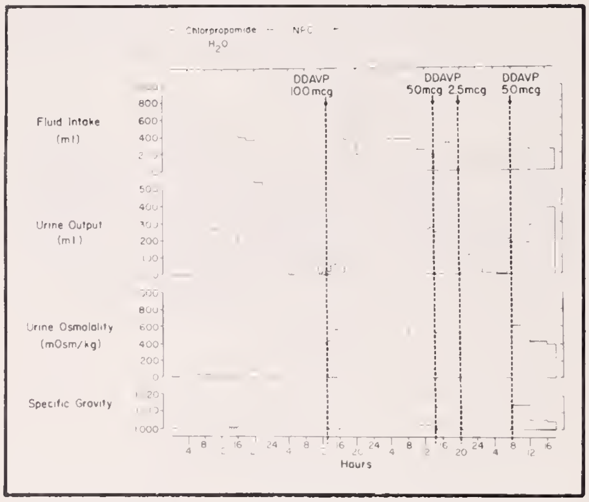

Fig. 5 — Patient #6 — DI secondary to head trauma. Three day sequential monitoring of fluid balance and urinary concentrating ability.

Many patients with DI have associated central nervous system abnormalities. In these patients an additional and desirable benefit from DDAVP has been reported by their families. Improved attitude and decreased mood swings have been consistent.

Follow-up laboratory studies were unchanged from pretreatment values, implying that DDAVP did not adversely affect the hematologic or hepatic systems. No specific adverse effects have been noted since the institution of DDAVP in any of our patients.

Discussion

Central neurogenic diabetes insipidus is characterized by significant polyuria and polydipsia as a consequence of deficiency of the neurohypophysial peptide, antidiuretic hormone. ADH is synthesized by neurons in the supraoptic and paraventricular nuclei of the hypothalamus. ADH is released from these neurons and transported by axonal flow to the posterior portion of the pituitary gland (neurohypophysis). Destruction of the hypothalamic nuclei or disruption of ADH transport along the hypothalamic pituitary neurofibers will produce the syndrome of DI. This condition may be partial or complete as well as transient or permanent. DI usually appears as an isolated disorder. However, variable degrees of anterior pituitary dysfunction may also be associated with DI. The type and degree of clinical manifestations produced are influenced by the nature of the underlying etiology. Invasive disorders such as neoplasms and histiocytosis X tend to produce permanent and generalized conditions. Posttraumatic etiologies tend to produce an isolated DI which is frequently transient and partial in nature. However, posttraumatic anterior hypopituitarism has been described and should always be considered in such patients.[1,2] DI has been described during the neonatal period and may be the first manifestation of an underlying metabolic or structural central nervous system disease.[3]

The traditional management of DI has utilized intramuscular injections of aqueous vasopressin (Pitressin, Parke-Davis), vasopressin tannate in oil (Pitressin Tannate in Oil, Parke-Davis), or intranasal administration of lysine vasopressin (Diapid, Sandoz). Each of these substances have disadvantages as well as potentially serious side effects (Table 3). Less severe cases have been treated with oral medications such as,

TABLE 3

Disadvantages of Alternative Antidiuretic Therapy

Aqueous Vasopressin	**Short duration of action** **Significant pressor activity** **Parenteral administration**
Vasopressin Tannate in Oil	**Variable control of fluid and electrolyte status** **Pain on injection** **Side effects (headache, abdominal discomfort)** **Pressor activity** **Abscess formation** **Allergic reactions** **Suspension difficulties; 30 minute preparation time** **Highly viscous; Requires Z-track injection**
Lypressin	**Short duration of action** **Pressor activity** **Local nasal mucosal irritation** **Gastrointestinal upset when swallowed**

thiazide diuretics, chlorpropamide, carbamazepine and clofibrate.[4-7]

DDAVP was recently made clinically available (Ferring Pharmaceuticals, Malmo, Sweden) for the treatment of DI. DDAVP is a synthetic analogue of vasopressin in which two modifications of the molecule result in a biologically improved compound (Figure 6). Deamination of the first amino acid increases the antidiuretic to vasopressor activity (AD/VP) and also prolongs the duration of action.[8] The prolonged duration of action of DDAVP may be related to resistance to enzymatic degradation, increased lipophilicity (which would increase distribution volume and decrease clearance), or to the smaller steric size which may facilitate its reabsorption by the renal tubles. Substitution of D-for L-arginine at the eighth amino acid also increases the antidiuretic to vasopressor (AD/VP) activity.[9] It has been demonstrated that DDAVP has an AD/VP ratio of 2000:1 as compared with arginine vasopressin which has a ratio of 1:1. The enhanced AD/VP ratio indicates that DDAVP has minimal or nonexistent pressor effects and makes DDAVP the most specific antidiuretic hormone clinically available.

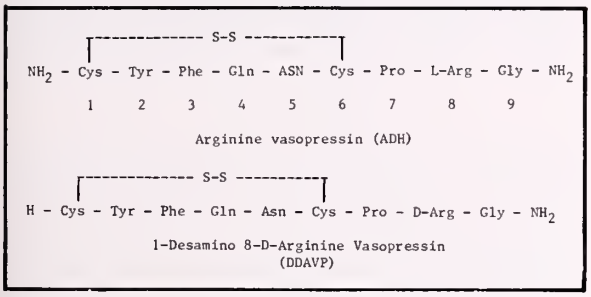
S-S
NH2 - Cys - Tyr - Phe - Gln - ASN - Cys - Pro - L-Arg - Gly - NH2
1 2 3 4 5 6 7 8 9
Arginine vasopressin (ADH)
S-S
H - Cys - Tyr - Phe - Gln - Asn - Cys - Pro - D-Arg - Gly - NH2
1-Desamino 8-D-Arginine Vasopressin
(DDAVP)

Fig. 6 — Structures of Antidiuretic Substances.

Absorption of DDAVP from the nasal mucosa is indirectly proportional to the dosage administered.[10] At therapeutic doses of 5-10mcg 10-20% is absorbed, at 20-40mcg 10% is absorbed, and at 160-320mcg only 2.5-5% is absorbed. In addition, the absorption from the nasal mucosa is slow which may prolong the duration of action of DDAVP. The pharmacokinetics of DDAVP have been studied in a limited number of patients by means of a specific radioimmunoassay.[11,12] Peak plasma levels occur at one to five hours with a duration of action of eight to twenty hours. This data reflects the broad range of elimination rates and daily dosages that are usually employed to clinically regulate DI.[13-15]

The duration of effect of DDAVP is dose related.[10] Therefore, most patients if given a sufficiently large dose could be managed with a single daily dose. This has the advantage of convenience, but the disadvantage of producing a prolonged period of relative oliguria, which could result in cerebral water intoxication. Twice daily administration should be achieved whenever possible since it provides a smoother regulation of polyuria. Individualization is then possible by tailoring the morning or evening dose to the patient's requirements. While the duration of effect is dose related, the effect on renal tubule concentrating ability is not dose related. Maximum urine concentration occurs after doses of 10mcg for infants and 20mcg for children.[16]

In our patients the initial dose of DDAVP produced a longer duration of action than subsequent doses. The first dose provided an antidiuretic effect for 10-24 hours and thereafter was clinically satisfactory for 10-12 hours. The mechanism for this initial effect may be due to DDAVP binding to renal tubular and collecting duct ADH receptors, which have been unoccupied because of ADH deficiency. This produces a prolonged antidiuretic effect which diminishes slowly. With subsequent doses, DDAVP would compete for receptor sites with the remaining membrane bound molecules and shorten the duration of action.

The kinetics of such competitive binding may be overcome by increasing the dose of DDAVP administered. Since the degree of antidiuretic effect and the duration of action does not produce a linear increase with increasing doses, DDAVP appears to follow the expected relationships for competitive receptor binding. This is speculation and the actual mechanism in our patients remains unknown.

Reported side effects related to DDAVP are uncommon.[13,14,17,18] Headaches can occur and may be related to the dose and a local nasal mucosal effect.[13] Other side effects include slight elevations in blood pressure, nasal congestion, and abdominal cramping. Water intoxication may occur in patients without an intact thirst mechanism.

DDAVP has been administered to pregnant women without reported problems.[19] DDAVP has advantages over pitressin in oil or lysine vasopressin because it lacks oxytocic activity and therefore will not stimulate uterine contractions. Data on the use of DDAVP in pregnancy is scarce and such patients should be followed closely.

Tolerance to DDAVP effects has not been observed in our patients, but has been reported.[13,20] The need for increasing DDAVP doses suggests that a change in response may be occurring. An antibody to DDAVP has not been identified.[13]

The ease of administration, improved fluid and electrolyte balance and elimination of major side effects have all contributed to increased psychological benefits for patients.[21] This may be on the basis of less dramatic fluid and electrolyte shifts within the central nervous system neuron.

Our experience, as well as that of others, suggests that DDAVP should be the drug of choice for the treatment of central neurogenic diabetes insipidus in pediatric patients.[11,13,14,17,18,22-24] Its ease and convenience of administration, long duration of action, purity and absence of side effects meets the criteria for an ideal therapeutic agent.

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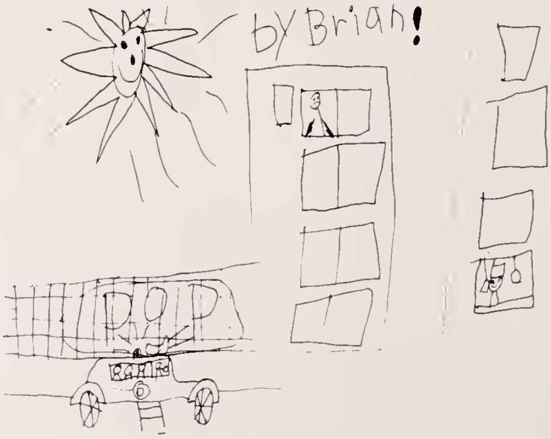

Febrile Convulsions

Current Controversies

JOHN T. MACDONALD, M.D.*

Infantile febrile convulsions continue to be the most common seizure pattern in the pediatric age group. While the basic pathogenesis remains unknown, a genetic predisposition seems probable. Only a very small group of affected infants later develop epilepsy. Treatment modalities and their effectiveness are controversial.

SINCE TWO to five percent of children will experience febrile convulsions, an understanding of the factors involved and treatment modalities available is important to any physician dealing with the pediatric age group. The clinical management of this common problem remains controversial. The diagnosis itself is at times made difficult by poor parental observation and recall of the event. By definition fever is present. Typically, the rectal temperature is at least 37.7°C, and the child demonstrates a period of unresponsiveness associated with eye-rolling or nystagmus, tonic or clonic movements of extremities, incontinence, generalized hypotonia, or postictal lethargy. Serious intracranial infections must be excluded.

Risk Factors

The population at risk for a first febrile seizure includes children from six months to three years of age. Most infants have some preceding viral illness, particularly upper respiratory or ear infections, pharyngitis, or Roseola. The convulsion commonly occurs as either the first symptom of the illness, or within 24 hours of temperature elevation.

The recent Collaborative Perinatal Study of 1706 children with febrile convulsions documents prolonged seizures (greater than 15 minutes) in 7.6%, recurrent seizures within 24 hours in 16.2%, and focal seizures in 4%.[1] Children with any of these three features were designated as having "complex" convulsions and found to have an increased risk of epilepsy (recurrent nonfebrile convulsions) by age seven years. The actual number of brief recurrent febrile seizures in neurologically normal children may not be a true risk factor for later epilepsy. In infants whose developmental or neurological status was abnormal prior to the onset of a "complex" febrile convulsion, the risk of subsequent epilepsy was eighteen times higher than in a normal population.

About 25 to 50% of children with one febrile convulsion will have a recurrence, usually within one year of onset.[1–2] At least ten percent will have over four episodes during their childhood. There appears to be an increased recurrence rate in those with onset under twelve months of age. The lowest recurrence rate (25%) includes children with onset between one and three years and a negative family history.

Livingston has attempted to separate "simple" febrile convulsions from "epilepsy triggered by fever".[3] His definition of the former included: (1) age six months to three years (2) duration less than 15 minutes (3) non-focal seizure (4) negative family history of nonfebrile seizures (5) EEG normal one week after episode. Only three percent of children with "simple" febrile convulsions later develop afebrile seizures. Therefore, it is suggested that continuous phenobarbital be reserved for those in the later group, i. e. those with prolonged, focal seizures or abnormal EEGs. Exceptions to Livingston's categories are common and Millichap has advocated "intermittent" phenobarbital at the onset of fever in any infant with febrile seizures.[4]

The prognostic value of the electroencephalogram (EEG) is controversial. Transient abnormalities related to the convulsive episode have been reported within the first week after a febrile convulsion; therefore, it is best to wait at least one week before testing the child. At this time there will be no evidence of an underlying chronic convulsive tendency in the vast majority of patients. Some authorities feel that a normal EEG is helpful in identifying those children with "simple" febrile convulsions which may not require anticonvulsant therapy. Others suggest that an EEG be deferred until a recurrent febrile convulsion occurs.

Pathogenesis

The prognostic value of the electroencephalogram vulsions remain unknown and neuropathological studies have been unremarkable. Speculation has focused upon the presence of dehydration with resultant osmolar shifts during rapid temperature elevations. Other suggestions include hypoglycemia following aspirin therapy or alcohol rubs, epileptogenic effects of high penicillin concentrations, and the known tendency of commonly prescribed decongestants such as diphenhydramine to activate an otherwise silent epileptogenic cerebral focus. While the peculiar vulnerability of the developing CNS to even moderate temperature elevations remains unexplained, some studies point to an underlying genetic basis compatible with an autosomal dominant pattern with incomplete penetrance to account for the well documented familial pattern of febrile convulsions.[2]

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Prognosis

While mortality is insignificant, long term morbidity remains a subject of dispute. It is known that permanent hemiparesis is very rare and most studies reveal no effect on IQ or later school performance.[4–5] The incidence of true epilepsy in this group of children is generally estimated to be 1 to 3%, significantly higher than the 0.5% incidence in the general population. Livingston's long term prospective studies indicate that 97% of afebrile seizures following febrile convulsions will occur by five years of age. Some retrospective reports, suggest a relationship between prolonged infantile febrile seizures and adult onset temporal lobe (psychomotor) convulsions.[6] Future prospective investigations of large groups of children may provide a better understanding of the relationshp between febrile convulsions and subsequent epilepsy.

Treatment

The justification for prophylactic drug treatment in this group of children is predicated upon the small but increased risk of later epilepsy and the possibility of brain damage resulting from prolonged seizures. It is presently unknown if drug therapy actually prevents later onset epilepsy. Many will therefore withhold treatment, particularly after the first episode, as only 25% will have a recurrence if the family history is negative. Even the vast majority of those with recurrences seem to suffer no subsequent neurologic or behavioral abnormalities.[1] In addition, common problems with phenobarbital, including poor compliance, overdosage, behavioral and cognitive side effects, and withdrawal symptoms with abrupt cessation of long term therapy are often considered by the physician who elects to defer treatment. Parental attitudes toward chronic medication also need to be evaluated.

The most common pharmacologic therapy has been "intermittent" phenobarbital given at the onset of fever.[4] Controlled studies fail to demonstrate any significant decline in recurrence rates with this regimen.[7–9] A major problem is the difficulty in rapidly establishing therapeutic blood levels with the usual oral dosage prescribed. Even with an oral phenobarbital dose of 10 mg/Kg/ day it may take two-four days to achieve effective blood levels, and with higher dosages the child's mental status may become compromised.[10]

The use of continuous phenobarbital, adjusted to maintain blood levels within the therapeutic range, has generally been proven more effective than intermittent therapy in preventing recurrences.[7–9] Only one study does not support this claim.[11] The usual dosage in infants is about 5 mg/Kg/ day given in two divided doses. The choice of daily, long term therapy remains controversial, especially when side effects are encountered. When problems such as hyperactivity or irritability are prominent, the substitution of mephobarbital (Mebaral) is sometimes successful. Other medications such as diphenylhydantoin (Dilantin) have been used but are generally considered much less effective than phenobarbital. Recent clinical trials in Europe suggest the effectiveness of "intermittent" rectal diazepam (Valium) at the onset of fever. Although this work has not been confirmed, it may prove to offer another alternative to continuous phenobarbital administration.[12]

Summary

The treatment of infantile febrile convulsions must remain an individual clinical decision based upon present medical knowledge. Even without chronic pharmacologic treatment, the overall prognosis following a febrile convulsion remains good. However, a small percentage of these children will later develop epilepsy and, on rare occasions, a child may suffer some degree of brain damage after a very prolonged febrile convulsion.[13] In those children at risk, i.e. those with prolonged or focal seizures, preexisting neurological problems, positive family history, age under one year, or abnormal EEG, the physician may elect to use phenobarbital prophylaxis. Treatment is usually terminated only after one seizure-free year, or when the child is at least four years old. Additional therapeutic approaches may be suggested as the results from long term prospective clinical studies become available.

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*References will be found on page 466.

Uncommon Inguinal and Scrotal Lesions in Infants

BERNARD J. SPENCER, M.D.*

In addition to the common lesions, infants can present with a remarkable variety of lumps in the inguinal scrotal area. A classification and discussion of the uncommon findings is presented and early diagnosis is emphasized.

EVERY PHYSICIAN WHO takes care of children encounters inguinal herniae, scrotal hydroceles and the various levels of testicular descent. The frequency of these lesions makes it all the more important to be aware of the less common lumps in the area to avoid pitfalls in their management. The purpose of this paper is to review the variety of inguinal and scrotal lesions in infants, and to emphasize the importance of early diagnosis rather than "watchful waiting" of any questionable ones.

Consider what dangerous delay could result from observing at intervals a hydrocele which was shielding an embryonal carcinoma of the testis! How easy it would be to mistreat an inguinal lump in a female infant as an enlarged lymph node when it can well be a prolapsed ovary in a small hernia in imminent danger of torsion and necrosis. Imagine the consternation of the surgeon who operates on a child for hernia and finds himself dealing with an inguinal lymphangioma instead. Such examples of delay, mistreatment and confusion are best avoided by appreciating the spectrum of pathology seen in infants.

Classification

Diagnosis of inguinal or scrotal lesions may be classified under four general headings.

I. Lesions representing variations in normal development
   - A. Hydrocele of the inguinal cord
   - B. Hydrocele of Canal of Nuck
   - C. Prolapse of ovary in hernia of female infant
   - D. Ectopic testis
   - E. Vestigial testis

II. Lesions from congenital malformation or aberrant tissue
   - A. Adrenal rest in inguinal canal
   - B. Renal embryonic rest
   - C. Ectopic splenic tissue
   - D. Hamartoma
   - E. Gonadal malformation

III. Lesions from inflammation, trauma or torsion
   - A. Neonatal meconium peritonitis of tunica
   - B. Neonatal infarction of testis
   - C. Abscess in scrotum from abdominal peritonitis in infant
   - D. Orchitis or epididymitis
   - E. Torsion of testis
   - F. Torsion of appendix testis
   - G. Posttraumatic hemorrhage and edema
   - H. Inguinal or iliac adenitis and abscess
   - I. Scrotal swelling from ventriculoperitoneal shunt.[1]

IV. Tumors, benign and malignant
   - A. Lymphangioma
   - B. Hemangioma
   - C. Varicocele of cord
   - D. Fibroma
   - E. Lipoma
   - F. Dermoid
   - G. Teratoma
   - H. Neurofibromatosis
   - I. Rhabdomyosarcoma
   - J. Embryonal cell carcinoma
   - K. Interstitial cell (Leydig) tumor
   - L. Neuroblastoma
   - M. Extrarenal Wilms' tumor
   - N. Malignant lymphoma, Hodgkin's and non-Hodgkin's
   - O. Carcinoid of Testis

Discussion

Some specific points relate to each of the groups above and help differentiate the various lesions.

In the first group, a hydrocele of the inguinal cord lies above and separate from the testis. It differs from a hernia in that it will not reduce, yet provokes no obstructive symptoms, is usually not painful and the examiner can feel the upper margin of the mass when the cord is pulled down by traction on the testis. The female analogue in the canal of Nuck is seldom seen.

Prolapse of the ovary in a hernia sac in a female infant is not uncommon, however, and must be recognized to avoid damage to the gonad. It feels like a small bean-shaped mass, usually 1 to 2 cm in length and is slightly mobile in the sac. It can be nontender unless edema or torsion jeopardizes the blood supply in which case it becomes tender and larger. A swollen, tender incarcerated ovary warrants surgical explora-

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*Department of Surgery, Minneapolis Children's Health Center; Clinical Professor of Surgery, University of Minnesota Medical School.

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tion; but the nontender movable one can be scheduled electively in the next day or so after it is seen.

Ectopic testis must be considered in a patient with an ipsilateral empty scrotum who has a mass palpable in the perineal area, lateral thigh or inguinal area, or even a double mass on the opposite side. Vestigial or atrophic testis should be predicted if one can feel a cord and vas beyond the external ring attached to a small, firm nubbin in the scrotum.

Lesions in the second group, arising from congenital malformations, or aberrant tissues are usually recognized during the course of routine herniorrhaphy or orchiopexy.

Adrenal rests are small, usually only a few millimeters in diameter. They are often mistaken for lobules of fat, but are recognizable by the characteristic orange-yellow hue of adrenal tissue. Renal embryonic rests are rarer still and may be discovered as part of a teratoma or otherwise identified by the pathologist. Both adrenal and renal rests have been the site of inguinal area tumors. Neuroblastoma has been seen in adrenal rests and extrarenal Wilms' tumors have been reported in renal rests.[2]

Ectopic splenic tissue may be seen occasionally hanging like a red berry along the inguinal cord or lying more flattened just above the testis. This tissue can have significance if splenectomy has been done for medical reasons and ectopic splenic tissue is overlooked.

Gonadal malformations require the information gleaned from hormonal assay, chromosome count, chromatin study, probably biopsy, and the expertise of the appropriate pediatric specialist before surgical management is completed. The lesions encountered may vary from a mature ova-testis to a primitive gonadal streak and correct care must be individualized according to the findings.

The lesions in group three resulting from inflammation, trauma and torsion can at times pose a diagnostic problem.

In the neonate, the telltale greenish-black hue of meconium visible through thin scrotal tissue denotes a meconium leak from a bowel perforation into the tunica below and establishes the diagnosis as meconium peritonitis. The testis is usually palpable and is not firm. If the testis is firm and the scrotum is discolored by a reddish-purple color in the neonate, one must suspect testicular infarction, torsion or a tumor. Surgical exploration should be done promptly.

In the infant, orchitis and epididymitis are unusual and one must always suspect torsion when a painful testis and erythematous scrotum is seen. Testicular torsion produces a swollen, very painful testis which is often a trifle elevated in the scrotum.

Torsion of the appendix testis is usually somewhat less painful and swollen, and the tenderness seems more at the upper pole of the testis. At times transillumination will identify the dark appendix testis in the expected location. Doppler ultrasonic measurement of blood flow in the testicular artery may help in the differential diagnosis between testicular torsion, torsion of the appendix testis and inflammation. It is usually diminished or absent in torsion, unchanged in appendix testis torsion and increased with inflammatory conditions. We use this device as a diagnostic adjunct because the findings are not consistent and thus we depend primarily on a careful physical examination, history and urine analysis to make the diagnosis. Unless torsion can be ruled out, surgical exploration is the prudent course.

Inguinal adenitis and the more rare iliac adenitis are accompanied by the classical signs of inflammation, fever, pain, tenderness and swelling in varying degrees. Careful history and examination will usually lead to a correct diagnosis without a need for surgery unless an abscess develops. Rarely, in the infant, an inguinal adenitis will so closely simulate an incarcerated ovary or incarcerated hernia that surgical exploration must settle the issue.

A varied spectrum of tumors may be encountered in the inguinal scrotal area as noted in group four. Considering the number of benign tumors seen about the body in infancy, it is not surprising to find an occasional hemangioma, lymphangioma, fibroma, lipoma or dermoid in the inguinal area. In the removal of these lesions it is most important not to injure the normal cord structures or testes to excise a benign lesion.

Varicocele is uncommon in infancy. Wilms' tumor on the left may present with a scrotal varicocele;[3] so an intravenous pyelogram should be obtained in a patient presenting with an unexplained left varicocele.

Although each of the malignant tumors in the inguinoscrotal area is uncommon, the combined varieties comprise a significant total number.

Embryonal cell carcinoma is the diagnosis most likely when malignancy occurs within the testis in infancy.

The most common soft tissue sarcoma in childhood is the rhabdomyosarcoma. Although this sarcoma can occur in a large variety of sites, a sizable number appear in the lower genitourinary tract in both sexes. The botryoid variety of rhabdomyosarcoma protruding from the vagina of an infant is well known, but not so familiar is the sarcoma arising along the distal cord or paratesticular tissues in the male.[4] In addition, sarcoma arising within the prostate or bladder may emerge to be palpable in the inguinal or suprapubic area.

There has also been increasing recognition of the incidence of malignant lymphoma in the testis. One of the parameters of following children under treatment for lymphoma is careful examination of the testis and biopsy is sometimes required.

Conclusion

A large variety of lesions may occur in the inguinal and scrotal region in infancy. The classification presented shows they may range from an innocent cord hydrocele to a highly malignant tumor of the testis.

There is no place for "watchful waiting" of an undiagnosed lump. Surgical exploration should be prompt for any lesion where one is unsure of the diagnosis or not entirely confident of the safety of delay.

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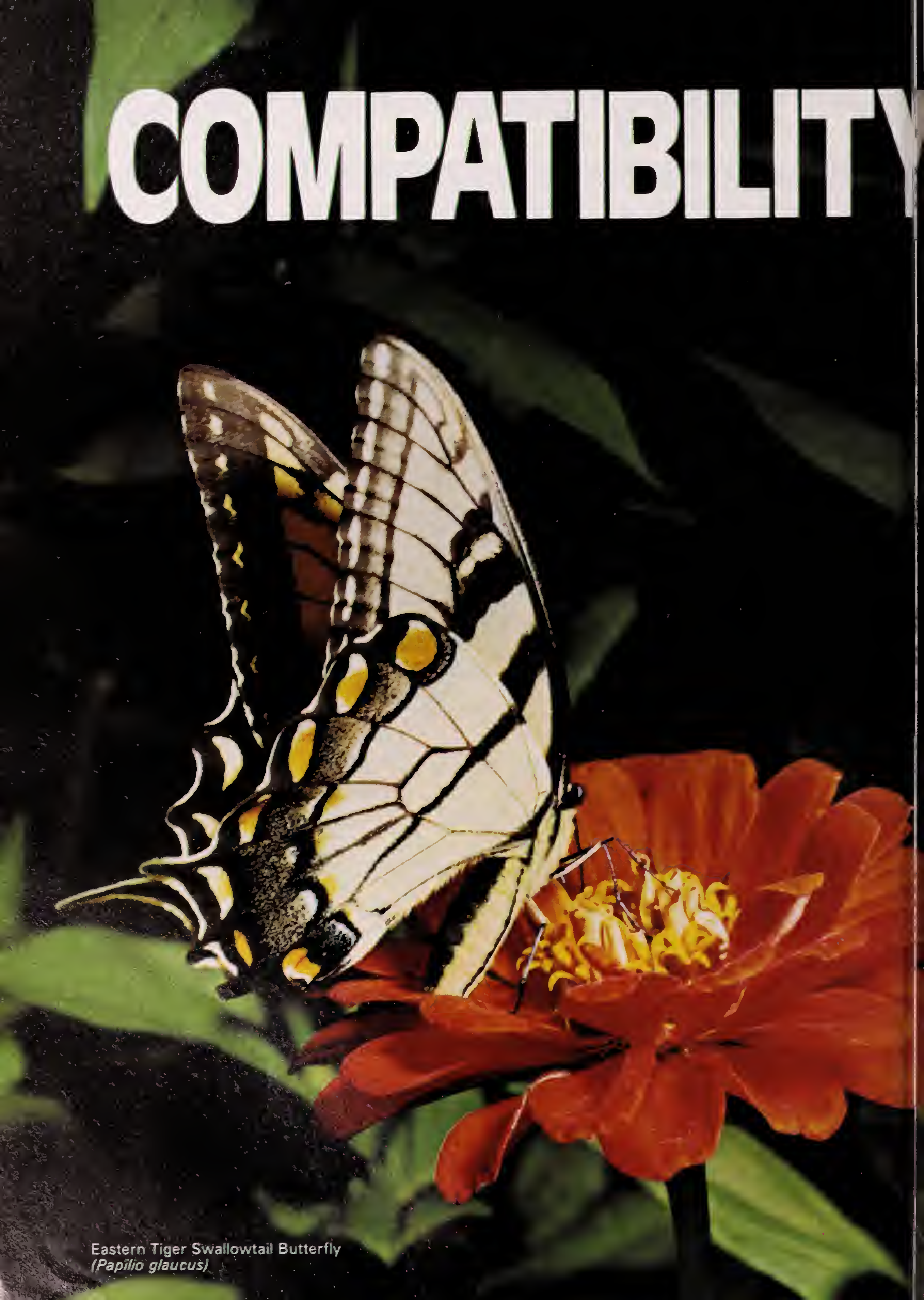

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Fetal Turner Syndrome

R. M. DRAKE, M.D.* and R. A. FRANCIOSI, M.D.*

The Turner Syndrome (XO syndrome) is a well known chromosomal disorder. Most of these patients die as fetuses, often without recognition of their primary disease. Two cases of the Fetal Turner Syndrome studied at the Children's Health Center in the past year are reported and the characteristic lymphedema and nuchal cystic masses are described. The importance of a careful necropsy examination of these fetuses is noted. Establishing the diagnosis will assist the physician and the parents in future family planning.

THE CLINICAL FEATURES of the Turner Syndrome in infant and child are well known. Physicians have a high level of diagnostic suspicion when dealing with these patients and confirmation is readily obtained by chromosome analysis. Also, it is well recognized that the 45 XO karyotype (Turner Syndrome) is the most common chromosome abnormality among abortuses. It is estimated that about 97% of those affected experience a spontaneous abortion.[1] In the XO fetus from ten to twenty-one weeks of development, large cystic hygromas of the neck and generalized edema are distinctive features. In the past year, in consultation, we have performed autopsies on two fetuses with the Fetal Turner Syndrome. These cases are reported and briefly discussed.

Case Reports

Case 1

A formalin fixed fetus weighing 411 grams and measuring 19 cm. crown-heel length was received in consultation. A previous, partial autopsy had been performed with evisceration of organs and incision of several cystic masses of the posterior and lateral neck. There was generalized lymphedema as well as a marked enlargement of the posterior and lateral soft tissues of the neck in which were a number of cystic spaces measuring up to 6 cm. in diameter (Figures 1 and 2). No malformations of skull or skeletal system were noted and this was confirmed by x-ray examination. Examination of the eviscerated organs revealed a hypoplastic tubular type coarctation of the aorta and a ventricular septal defect. There was a Meckel's diverticulum and a hypoplastic gall bladder. The ovaries, fallopian tubes and uterus were present and of normal size and shape. The placenta weighed 434 grams and measured 17 x 16 x 3 cm. There was a single umbilical artery in the umbilical cord. The maternal surface was pale gray, soft and friable. No vesicles were present. Microscopic examination revealed numerous hydropic villi, but no vesicles.

The gestational history was of a 30-year-old gravida one, para one admitted to the hospital when she noted a gushing of fluid from the vagina. Her last menstrual period had been four and a half months previous. Six weeks before admission, her uterus appeared enlarged and an ultra-sound examination revealed an increase in the size of the placenta. No fetal movements were ever felt. An 8 x 6 cm. fluid-containing cystic structure was noted below the fetus. Hysterotomy was performed the day following admission with the removal of the fetus and an enlarged, soft and somewhat friable placenta. Twenty-four hours before surgery, an HCG of 318,976 IU was obtained on a 24-hour urine specimen. A serum value was 5,800 ng/ml. with a second trimester normal range of 2,040 to 6,122 ng/ml.

Case 2

A moderately macerated fetus weighing 575 grams and measuring

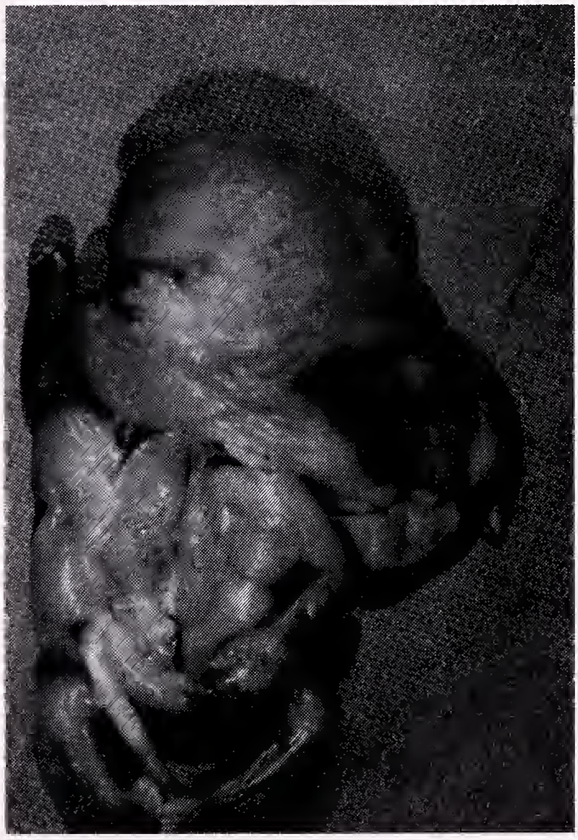

Fig. 1 — Anterior view of Case #1 after initial autopsy examination exhibiting the massive neck masses.

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*Department of Pathology, Children's Health Center and Hospital, Minneapolis, Minnesota.

26.5 cm. crown-heel length was received in consultation. There was marked generalized lymphedema, especially prominent over the dorsum of hands and feet together with extensive swelling of soft tissues of neck and posterior and lateral aspects of head containing multi-cystic spaces measuring up to 3 cm. in diameter. These contained clear colorless fluid (Figure 3). An alpha fetoprotein (AFP) value of 583k IU/ml was obtained from fluid aspirated from a cyst. A tubular type of coarctation of the aorta as well as a fused horseshoe kidney were present. Ovaries, fallopian tubes and uterus exhibited some autolysis but no structural abnormalities. Two umbilical arteries were present. The placenta was not available for examination.

The gestational history is that of a 28-year-old gravida 2, para 0 whose first pregnancy ended with a first trimester spontaneous abortion. In this present pregnancy, vaginal bleeding occurred early in the first trimester but ceased at 12 weeks. Normal fetal growth occurred with appropriate quickening and appearance of fetal heart tones. At 20 weeks gestation uterine contractions were detected. Bed rest and vasodialin therapy were followed by cessation of uterine contractions. Ultra-sound examination did not detect any evidences of placental abruption. A feto-gram was normal, and no bone anomalies were noted by x-ray examination. Five days later no fetal heart sounds were noted. Ultra-sound examination confirmed the fetal death. Twenty four hours after installation of 40 ml. of protaglandin F-2 alpha, a macerated female fetus was delivered.

Comment

Although neither sex chromatin nor karyotype examination was performed in these cases, the generalized edema and a large nuchal cytic mass are characteristic features of 45 XO fetuses.[5,6] Cardiovascular, kidney and other anomalies are also commonly present. The edema and cystic hygromas appear to be consistent features in XO fetuses of age 10 to 20 weeks.[6] The neck lesions appear to be the precursor of the webbed neck seen immediately after birth and in older children.[7] A malformation in lymphatic development appears to be the underlying defect leading to the lymphedema and the nuchal cystic lesions.[9]

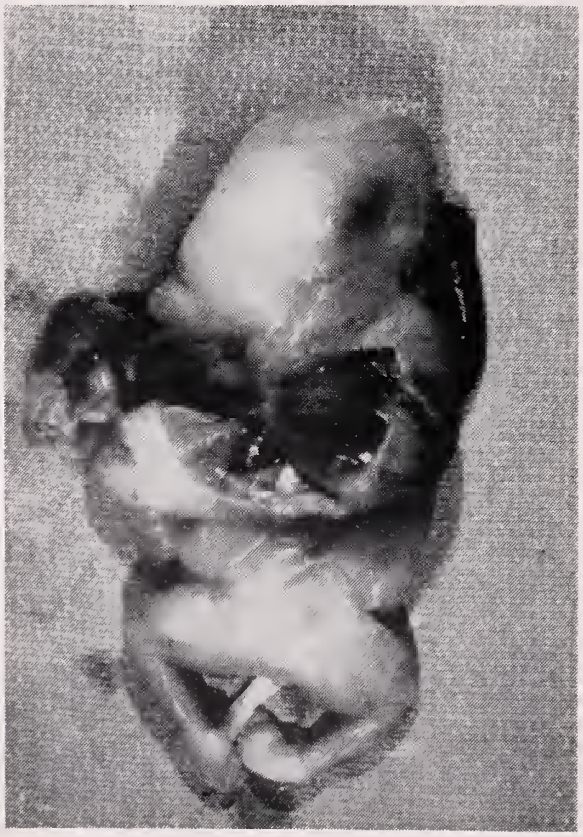

Fig. 2 — Posterior view of Case #1 demonstrating the fluid filled cystic masses of the posterior and lateral neck.

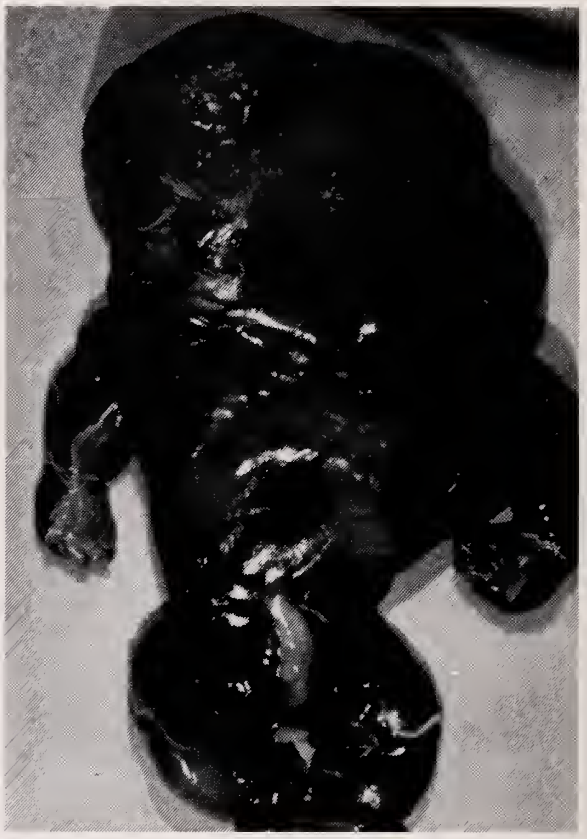

Fig. 3 — Anterior view of Case #2 exhibiting severe generalized edema and massive nuchal swellings.

The differential diagnosis would include hydrops fetalis either due to isoimmunization or the idiopathic type of hydrops. Blood group antibody studies or hemoglobin electrophoresis may be helpful in excluding these diagnoses. An encephalocele could be excluded by autopsy examination including x-rays.

The elevated alpha-fetoprotein level obtained from the aspiration of a cyst in Case #2 supports the suggestion that high levels of AFP in amniotic fluid reported in some cases of Turner Syndrome may result from aspiration of a cyst during amniocentesis.[8] While a careful autopsy is most useful in suggesting diagnosis of the Fetal Turner Syndrome, sex chromatin determination from smears made from amnion or bladder mucosa and/or chromosome analysis provide confirmation. A diagnosis is important for genetic counseling as the Fetal Turner Syndrome does not offer an increased risk to successive pregnancies as would be the case with Rh disease or neural tube malformation. We have identified eleven cases in the medical literature,[2,4,6] but it is thought that this malformation occurs more commonly than is appreciated.[3] Clinical awareness together with an autopsy can establish this diagnosis and thus assist in the counseling of parents for future pregnancies.

Acknowledgment

The authors wish to thank Drs. Richard Lynch and Ronald Peterson for the opportunity to study these cases.

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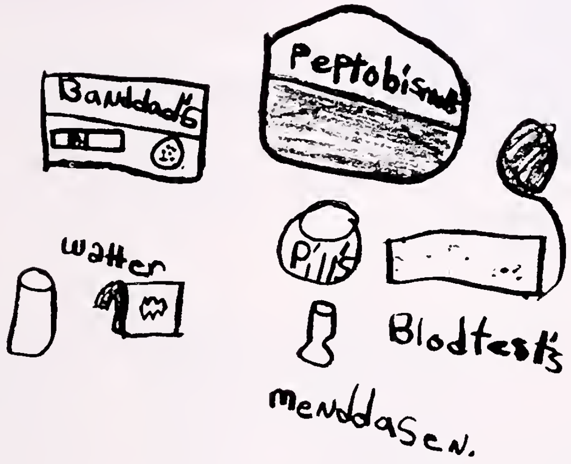

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Diagnostic Uses of Anorectal Manometry in Pediatrics

FELIX A. MCPARLAND, M.D.* and KAREN OLNESS, M.D.*

Anorectal manometry is a practical diagnostic technique in assessment of constipation in infancy and childhood. Its use is as reliable as a barium enema in ruling out Hirschsprung's disease. Our results suggest there is no need to do a rectal wall biopsy in the presence of a normal recto-anal reflex.

THE FREQUENCY of constipation in infancy and childhood justifies the investigation of all methods which contribute to the establishment of an exact diagnosis.

History

Barium enema was the first objective method of evaluating this spectrum of conditions. The normal to narrowed distal segment with a flair into the dilated upper segment is diagnostic of aganglionosis while the colon dilated all the way down to the sphincter muscles is typical of severe functional constipation.

Rectal wall biopsy was the next major refinement to be added to our armamentarium. If an adequate specimen (which extends more than 3 centimeters above the skin mucous membrane junction) is obtained for examination and no ganglion cells are seen, the diagnosis is absolute. Anal manometry has been a recent addition to methods of evaluating constipation.

This article will review the application of anal manometric assessment of recto-anal reflexes via balloon manometry in prematures, full-term newborns, and older children who have a history of constipation.

Physiology

Fecal continence results from resistance to outflow created by two muscle groups; the smooth muscle of the internal anal sphincter and the striated muscles of the pelvic floor and external anal sphincter. The internal anal sphincter is the thickened terminal portion of the rectal wall. Distention of the rectal wall causes reflex relaxation of the internal anal sphincter and this is known as the recto-anal reflex. This reflex allows descent of stool into contact with the upper end of the anoderm and normally triggers external anal sphincter and pelvic floor muscle contraction which results in defecation.

The relaxation of the internal anal sphincter in response to increased rectal pressure was first shown in 1877 by Gowers.[1] This remained an interesting physiologic reflex but of no clinical signifcance until 1964 when Callaghan and Nixon[2] reported that this reflex was absent in Hirschsprung's disease. Nixon, in collaboration with several other authors, has continued to demonstrate increasingly refined methods of investigating anorectal physiology.

Sphincter pressures may be recorded with open catheters, balloons over the catheters or by very small strain gauges. The open end catheters have the disadvantage of becoming occluded frequently if not constantly perfused with saline or water. Strain gauges are expensive and more delicate than catheters. For these reasons and to simplify the procedure, we have used only air or water filled balloons.

Rectal stimulation can be induced by rectal dilatation with open end catheters or balloons. For ease of ending the stimulus as well as making possible repeated stimuli at frequent intervals we have used only balloons.

Several authors reported that the recto-anal reflex was normally present in the smallest of newborns. However, in 1977, Ito, Donahoe, and Hendren demonstrated that this response was not uniformly present in prematures and newborns until the 39th week of gestation or the weight of six pounds had been attained.[3] In August, 1978, Meunier, Marechal, and Mollard[4] from Leon, France, surveyed over 200 applications of anal manometry and found, in the neonatal period, that their percentage of error was 26 percent including false positive and false negative results. They noted that, after the age of two years, the

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*Pediatric Surgeon, Minneapolis Children's Health Center and Clinical Professor of Surgery, University of Minnesota.

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results were consistently accurate in more than 98 percent of cases.

Since 1975 we have had the capability at Minneapolis Children's Health Center of studying the recto-anal reflex in infants and children via anorectal manometry. Our intent in developing this capability was to increase the sensitivity of prebiopsy diagnosis of Hirschsprung's disease, to reduce unnecessary biopsies, and to use the reflex as a basis for biofeedback to older children suffering from intractable constipation and soiling. Children generally tolerate the procedure well.

Method

After initial evaluation via history, physical examination, and appropriate laboratory studies the patient is placed in a supine position on an examining table. Infants occasionally require sedation. Prior to the procedure, a Fleet's enema is given to children of six months or older. A double balloon tied around a hollow plastic tube is inserted into the child's anus. Each balloon is connected to recording equipment via a pressure transducer. Recording equipment includes an oscilloscope, chart recorder, and a series of amplifiers all of which are easily visible and explained to the older child. The balloons are inflated with 5 cc of air. A third balloon is positioned above the two balloons and inflated with 20-30 cc of air intermittently while the anal sphincter responses are recorded.

Results

In 110 patients we have not yet obtained a normal reflex, i.e. relaxation of the internal sphincter with inflation of the rectal balloon, in a patient who later proved to have aganglionic megacolon. However, we have on occasion, failed to obtain a definite relaxation of the internal sphincter in children with normal innervation. Therefore, we have found it advisable to divide patients into three groups: (1) Normal recto-anal reflex, (Figure 1): (2) Absent reflex with mass contractions diagnostic of aganglionosis, (Figure 2); and (3) Non-diagnostic or no reaction to stimulation. (Figure 3). It is our clinical impression that the non-diagnostic reflex is most frequent in children who have had many years of constipation and fecal retention with an x-ray picture compatible with

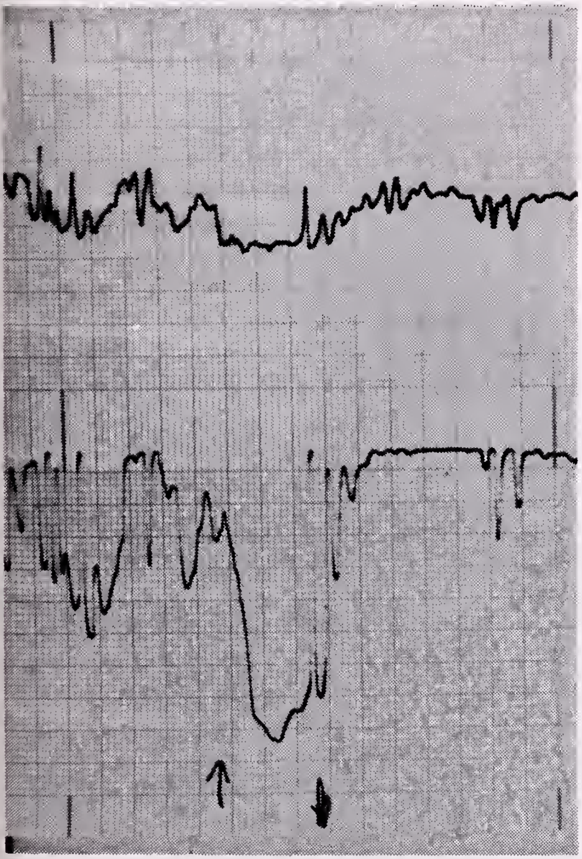

Fig. 1 — Normal recto-anal reflex. The internal sphincter relaxes after inflation of stimulating balloon.

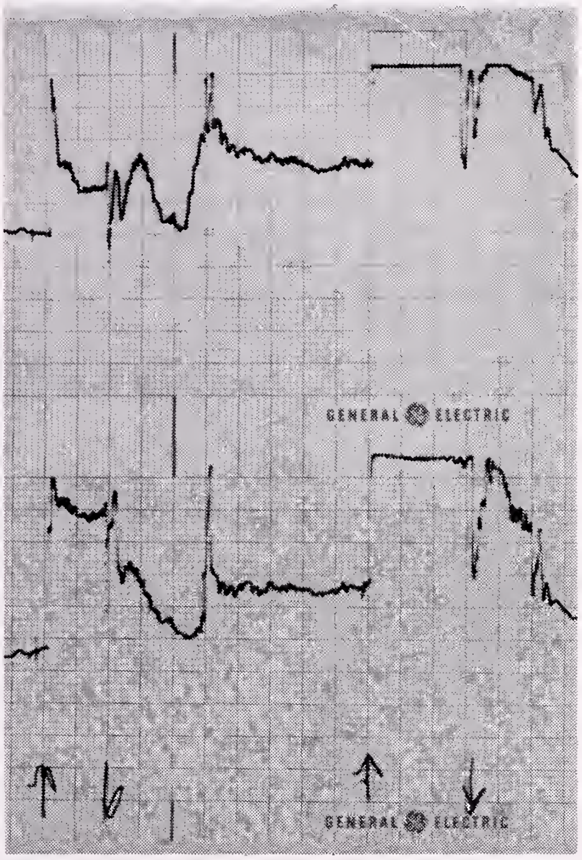

Fig. 2 — Aganglionosis. Note mass contraction of internal and external sphincters with stimulation.

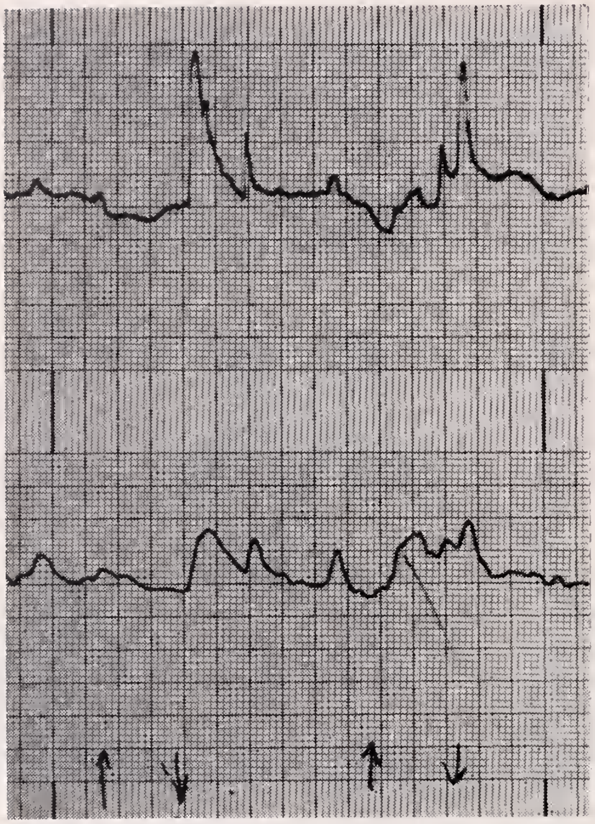

Fig. 3 — Non-diagnostic tracing. Note variable response to stimulation.

function constipation and in small premature infants.

With respect to premature infants and full term neonates our results have been diagnostic in approximately 75 percent of the patients, i.e. either a normal reflex is elicited (Figure 1) or a mass contraction response, diagnostic of aganglionosis, is obtained (Figure 2). About 25 percent have either no response to stimulation or have a response so variable that a definite diagnosis cannot be made safely.

In 1974 Engel et al. reported the successful treatment via operant conditioning of a six-year-old child who had lifelong fecal incontinence due to myelomeningocele and who had no recto-anal reflex initially.[5] With respect to giving children feedback from their recto-anal reflex we have found it useful but not essential to success with the biofeedback training program. Children with little or no fecal control following the repair of the supralevator type of imperforate anus often had no recto-anal reflex. Nonetheless, when fed back voluntary anal muscle responses, they rapidly developed fecal continence. Several patients, with long histories of functional constipation, had no initial response to stimulation, did well in training sessions, and subsequently demonstrated normal recto-anal reflexes.

The non-diagnostic response in children with functional constipation may be on the basis of huge dilatation of the rectum so that larger than usual amounts of air would be necessary to trigger relaxation of the internal anal sphincter or on the basis of insulating the rectal wall from the effect of the stimulating balloon by stool. Certainly, the natural history of these patients is that they retain huge amounts of stool without apparent response to recto-anal reflexes. After frequent defecation is established on a voluntary basis, the rectal diameter decreases and insufflation of air into the diagnostic balloon can elicit a normal reflex. It is anticipated that use of more sensitive equipment will make it possible to move some of these patients out of the non-diagnostic category.

The non-diagnostic response in neonates may be due to the lack of maturation of the ganglion cells shown experimentally and clinically by Smith.[6]

Conclusion

The use of anal manometry is as reliable as a barium enema in ruling out Hirschsprung's disease. Our results suggest there is no need to do a rectal wall biopsy in the presence of a normal recto-anal reflex. The response in children who do have aganglionic megacolon is diagnostic and can be confirmed by biopsy. In an infant who has constipation associated with a non-diagnostic reflex we would recommend a barium enema and consider a rectal wall biopsy. In an older child, who had a long history of constipation and soiling, and a nondiagnostic reflex we would recommend a treatment method without a rectal wall bisopsy or barium enema. If the patient then established normal bowel habits, the recto-anal reflex should return to normal.

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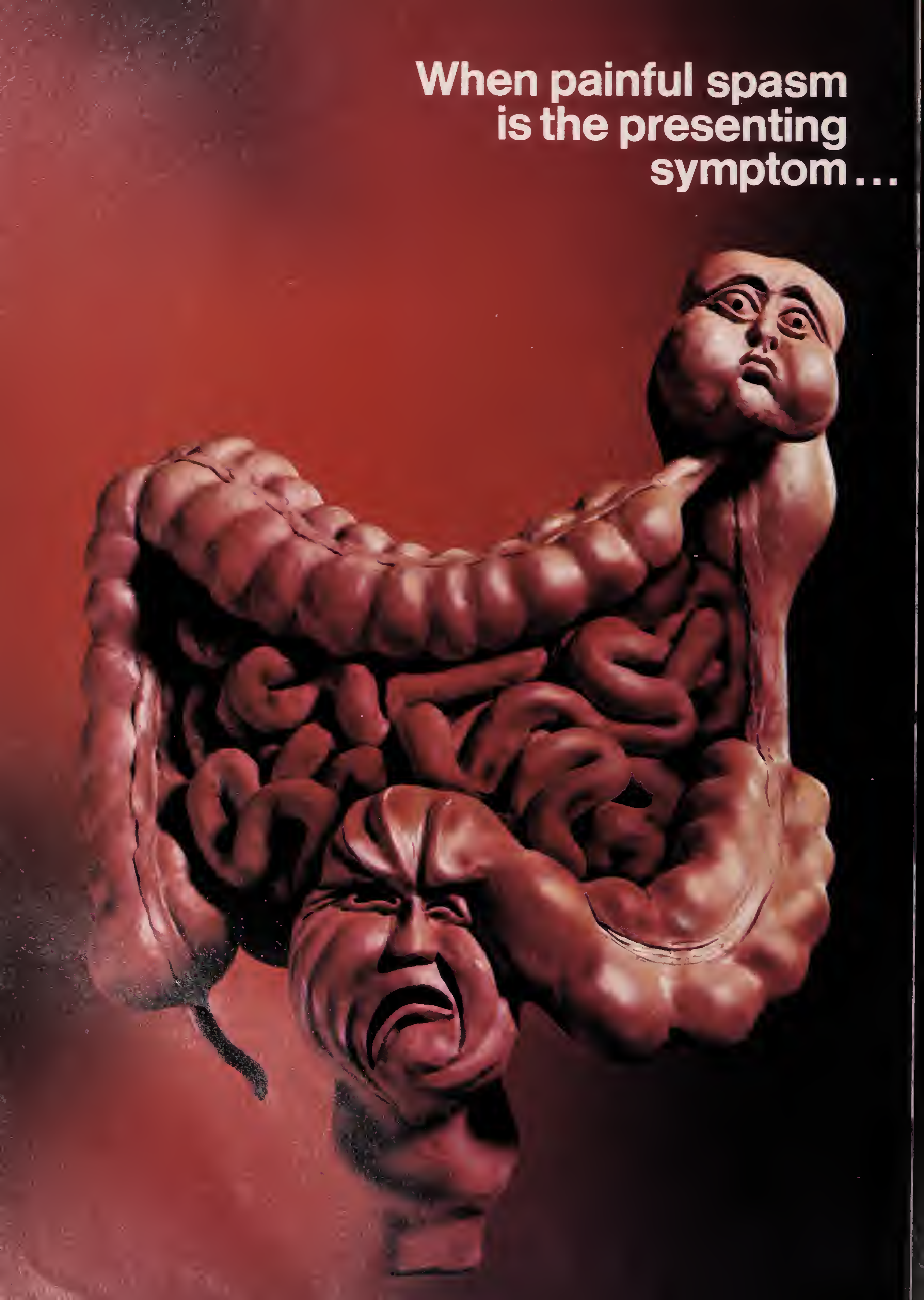
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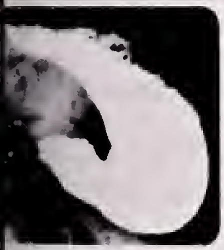

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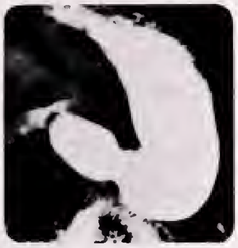

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Brief Summary

INDICATIONS
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage; severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis, cycloplegia; increased ocular tension; loss of taste, headache, nervousness; drowsiness; weakness, dizziness; insomnia; nausea; vomiting, impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

Usual Dosage: Bentyl 10 mg capsule and syrup: *Adults:* 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children:* 1 capsule or teaspoonful syrup three or four times daily. *Infants:* ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg. *Adults:* 1 tablet three or four times daily. Bentyl Injection: *Adults:* 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

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Idiopathic Thrombocytopenic Purpura in Childhood

LAWRENCE J. SINGHER, M.D.*

Idiopathic thrombocytopenic purpura is a common disease encountered in medical practice. The adult and pediatric entities differ greatly in their prognosis. Only recently has a better understanding of the etiology and the disease process been understood.

THE ENTITY OF Idiopathic Thrombocytopenic Purpura, (ITP), sometimes referred to as autoimmune thrombocytopenic purpura or post-infectious purpura, is a disease commonly seen in pediatric patients. ITP is in most instances a benign self-limited disease. Spontaneous recovery usually occurs within a short period of time.[1] It is most accurately defined as sudden onset of purpura, marked platelet decrease, and no marrow-associated abnormality. This is due primarily to the increased peripheral destruction of platelets. It must be noted that recent reports indicate a decreased megakaryocyte production as well.[2]

Numerous reviews of this disorder are found in the literature pertaining to diagnosis, management, and prognosis.[1,3,4,5] The lack of consensus as to proper therapy is noted and is often a source of frustration to the physician. Therefore, in this brief review, an attempt will be made to clarify relevant facts pertaining to Idiopathic Thrombocytopenic Purpura.

Etiology

The etiologic mechanism or factor causing this disorder is not fully understood at this time. Current opinion is usually influenced by adult ITP with its more apparent autoimmune basis. The etiology, pathogenesis, and prognosis of pediatric ITP differs markedly from the adult process.[6] In many of the pediatric cases it is likely that the platelet membrane is altered by the virus or by soluble viral antigen-antibody complexes. The affinity for sites on the surface of the platelet results in increased susceptibility to rapid destruction in the spleen and other areas of the reticulo-endothelial system. Childhood ITP seems most often incited by infection or post immunization reaction. The former is noted in up to 85 per cent of cases reported by Lusher.[1] In the majority of cases a two to three week antedative infective history is recognized. However, since infections are so commonplace in the pediatric population this premise is not totally accepted. The disorder is seen most often in winter and spring; the peak age range is two to eight years. Sex incidence is equal in this group and contrasts with the fifteen years plus age group in which females exhibit an incidence four to five times higher than males. In contrast with other racial groups, Caucasians manifest a higher incidence of the disorder.

As noted in Table 1, ITP can be broken down into four basic areas. ITP may occur in the prodrome to a disease, during the illness, or most commonly, shortly thereafter. Examples of activators may be an URI, exanthematous infection (rubeola, rubella, varicella), mumps, infectious mononucleosis, or cat scratch fever. Cytomegalovirus and hepatitis have also been reported in the literature. Numerous post immunization ITP cases have been reported. The reaction to rubeola vaccine appears to be the most common.[3] Platelet count drops within three to eight days are reported in 50 per cent of patients receiving this vaccine. Recovery usually occurs within three weeks time.[7] Medications such as chlorathizides, cephalosporins, digitalis, sulfas, and quinidine are also implicated as causative agents.[3] McClure noted that up to 3 per cent of patients would have some other

TABLE 1

ITP Etiology

***1. Postviral**
***2. True ITP**
No precipitating or associated illness
3. Association With Other Autoimmune Disease (Lupus, Graves, Rheum. Arth., Nephritis)
4. Drug Induced

***1. and 2. account for 95% of ITP**

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autoimmune disease, either in conjunction with, or after having had ITP.[3] The ruling out of diseases such as aplastic anemia and other malignancies must be taken into consideration in the pediatric patient.

Although the entity has been recognized for a long period of time, it was not placed on an immunologic basis until Harrington's experiments.[8] Early in the 1950s Harrington bravely infused himself with plasma from a patient with ITP. He sustained a profound thrombocytopenic effect, thus showing a transmissable antibody presence. This antibody since has been shown to be a 7S IgG type found in at least two-thirds of adult patients and in a significant number of pediatric patients with this disorder.[9,10,11] Research by Wybran in the 1970s has demonstrated the likelihood of cell-mediated immunity to autologous platelets, to be a pathogenic factor as well.[12] The overall picture is that of an agent combining with the platelet, thus inducing an antibody reaction.

Presentation

The presentation of ITP is usually that of an acute onset of petechiae and eccyhmoses. Children normally manifest bruising in trauma areas such as the shin and forearm, but bruising in other body areas signals abnormality. While families may not view minimal bruising as abnormal, the diffuse nature and progression of bruising makes recognition inevitable. A review of 305 patients by Jeanne Lusher shows the most common presenting signs and symptoms (Table 2).[1] The discovery of a slightly enlarged spleen is found in 5 to 10 per cent of patients (not unlike the normal population) and may reflect in many a postviral occurrence. Marked organ enlargement should alert the examiner to the possibility of a more serious disease.

The platelet count is decreased to under 40,000 in 80 per cent of patients and is less than 25,000 in 65 per cent.[4] Examination of the blood smear shows the platelets to be large in appearance, single, and often bizarre in shape. The larger size denotes the youthfulness of the platelets as compared with the more common, smaller size of mature platelets. At diagnosis 20 per cent of patients are found to be mildly anemic secondary to blood loss.[4] Often a mild lymphocytosis is discovered with occasional neutropenia noted. Eosinophil increase in the marrow or peripheral smear is no longer felt to be of clinical significance. Coagulation studies are normal with the one exception being platelet-vascular testing. The bleeding time is abnormal (reflecting platelet counts of under 50,000 to 100,000). This test is contraindicated since excessive bleeding, which may even necessitate transfusion, may occur. Tourniquet and clot retraction studies are like-wise abnormal due to platelet and blood vessel abnormality. A good correlation between bleeding time and platelet count does not exist. This is due to a defect in capillary function which is also noted in ITP. Thus contraction of the blood vessel is also found to be abnormal. Even with a normal platelet count purpura may exist, or conversely, bruising may clear rapidly in spite of a low platelet count.

TABLE 2

Findings In 305 Children With ITP

1. Epistaxis	83(28%)
2. Gross Hematuria	16(5%)
3. Spleen Tip Palpable	25(8%)
4. Shotty Adenopathy	190(62%)
5. Rel. Lymphocytosis	245(80%)
6. Eosinophilia	60(20%)

Khalifa in 1976 suggested that immunoglobulin abnormalities may have prognostic value in differentiating acute and chronic ITP.[13] Low IgA was more likely to be associated with patients ultimately having chronic ITP. Platelet testing for antibody has been done utilizing over twenty different tests. Complement fixation testing has shown 50 to 60 per cent of adult patients to have positive tests. A significantly lesser number of pediatric patients have had positive results with this test.[3] Platelets with Chromium^{51} tagging show decreased survival. This study, however, has not been totally accurate in the localization of sequestration areas in the body by scanning.[14] Pastakia has recently discussed a new aid in such localization through the use of Indium scanning.[15]

Bone marrow examination shows the megakaryocytes to be normal in quantity and appearance although decreased or absence of budding platelets is noted. This denotes either decreased platelet production or maximal release to the periphery. Since no platelet pool exists in the marrow and no margination occurs on the blood vessel, maximal circulation of platelets is found. The exception to this is the spleen where normally upwards of 30 to 35 per cent of the peripheral platelet pool may be found. These platelets tend to be younger, larger, and more hemostatically adept. The lifespan of platelets in the circulation is noted to be dramatically decreased in ITP from the normal duration of eight to ten days. .The ITP lifespan is reduced to a few days and in some severe cases, to hours or even minutes.

Prognosis

As mentioned previously, the platelet in this disorder is modified by the presence of an autoantibody and removed from the circulation by macrophages — particularly in the spleen. Studies by Baldini and Najean have shown significant differences between the adult and childhood prognosis.[16,17] Patients less than fifteen years of age show a predominant liver focus of sequestration only 4 per cent of the time. This is significantly different from the adult who shows primary liver focus 48 per cent of the time. Conversely the pediatric patient manifests exclusive splenic sequestration over 81 per cent of the time. This is the most obvious difference in the prognosis of the various age groups. Differing from the adult group where only 25 to 30 per cent spontaneously remit, the pediatric patient is able to effect this in the vast majority of instances. Within thirty days 50 per cent of childhood cases have resolved and by four months post diagnosis 80 per cent have recovered without therapy. A year after disease initiation over 90 per cent show normality. A few patients have been reported remitting three to four years after diagnosis. The noted rapid improvement reflects that the IgG antibody, without further antibody stimulus, gradually weakens. Since the IgG antibody half-life is known to be twenty-three days, rapid improvement is to be expected and is seen in the majority of cases.[18] Less than 5 to 10 per cent of pediatric patients go on to exhibit a chronic type of disease. This is manifested by persistent thrombocytopenia lasting a minimum of six to twelve months duration.

Reviewing ITP cases permits a suggestion of those patients most likely to have a chronic type of disorder. These are depicted in Table 3. Up to half of chronic patients will have a remission after splenectomy. Additional children will show improvement with immunosuppressive therapy. The few patients who exhibit a minimal response either as a function of time or therapies, seem to display minimal morbidity. The mortality of the disease has consistently been shown to be less than 1 per cent. This occurs predominately within the first week and is a rarity after the first month. A serious but rare complication and essentially the only cause of death is intracranial hemorrhage. The chance of this occurring has initiated discussion as to the need for therapy particularly during the acute phase of the disease.

TABLE 3

Increased Incidence of Chronic ITP

1. **No Preceding Viral Illness**
2. **Moderate Low Platelet Count at Onset (20,000 — 75,000)**
3. **Low IgA**
4. **Female**
5. **Over Ten Years of Age at Onset**

Therapy

Active therapeutic intervention into a disorder which has a low rate of complication and which usually will resolve spontaneously, has lead to much controversy and debate. Thus it continues to be difficult to assign an accepted methodology of treatment. While the goal is complete resolution of the process, the first priority is providing the patient with sufficient platelets for hemostatic normality for normal daily activity. Therapy can be broken down into five basic areas as noted in Table 4.

TABLE 4

Therapy for ITP

1. **Non-intervention**
2. **Steroids**
3. **Surgery (acute, chronic)**
4. **Immunosuppression**
5. **Transfusion**

The concept of non-intervention as expressed by Lusher advocates spontaneous correction via the patients' own mechanisms.[1,6] Protection of the patient, restricting activity, and preventing trauma is the thesis. Drugs that can cause unwanted complications or increase bleeding risks, (e.g. aspirin) should be avoided. Hospitalization is advocated if the child is young, if the platelet count is under 20,000, and if bleeding is occurring. The hospitalization continues until stabilization or increase of the count occurs.

Arguments for active intervention involving the use of steriods are noted in many articles.[4,5,19,20] Since the illness seems to be due in many cases to macrophage function increase, antibody production, and accelerated phagocytosis, the logic of attempts to decrease this are legitimate. Attempts are made to decrease such production and to reduce platelet removal by the RE system. The improvement of vascular integrity is emphasized. These facets are not well supported in studies reported pertaining to steroid use. Steroid usage has not been shown to increase onset of recovery nor long term prognosis.[1] Lusher, in her series, reports no instances of intracranial hemorrhages. Nine deaths have been reported in England in spite of the patients having received cortisone therapy[5] and no evidence supports the premise that cortisone prevents nervous system bleeding.[3] Steroids may, in fact, suppress platelet production and increase catabolism.[6,1] Patients have shown improvement only after steroids are discontinued in some reports. Steroid failure is noted in patients with a predominant hepatic focus. Most hematologists agree that if no spontaneous platelet response greater than 50,000 is noted by eight to twelve weeks, a three-to-four week trial of steroids is indicated.[21] Prednisone in a dosage of one-to-two milligrams per kilogram is most often utilized. Administration of prednisone in doses as high as four milligrams per kilogram, usage of Acth, or reattempts of steroids after initial failure have been reported successful by some.

It is well to note that if steroids or active treatment is to be effected, it is imperative to obtain *bone marrow aspiration* first. This procedure is indicated in order to eliminate the possibility of another bone marrow process of a more serious nature. Examples of this were two cases referred to this author. In both cases an erroneous diagnosis of ITP could have been prevented by bone marrow examination. I feel that all patients need such a procedure thus providing physician reassurance and increased parent confidence.

The third consideration of therapy is splenectomy. Studies by Baldini suggest that the spleen in all probability has a dual role in ITP.[16] The two functions are the production of autoantibodies and destruction of antibody coated platelets. Two reasons exist for splenectomy: acute bleeding circumstances or chronic presence of disease. In the acutely bleeding patient such a procedure may be lifesaving. Usually splenectomy may be performed without use of platelet transfusion. Standby of such is indicated especially if the platelet count is under 20,000. Since platelets are normally sequestered in the spleen, ligation of the splenic artery will allow infusion back into the systemic circulation. The concern of excessive platelet increment post surgery is felt to be unwarranted even when platelet counts exceed a million. Peak level is reached within four to fourteen days after surgery and levels off after that time. Optimum prognosis is found in the patient who reaches counts exceeding one-half million rapidly after surgery. Relapse is rarely noted in such cases. A number of patients resistant to full remission after splenectomy have been found in later trial to be more sensitive to agents such as steroids. When used as initial therapy 85 per cent of patients show remission after splenectomy. It is difficult to predict success of splenectomy in the chronic patient. Murphy and Lusher both note that no preoperative study can predict success but that upwards of 50 per cent of such patients will show remission after a chronic disease phase is found.[1,14] Post surgery the implementation of prophylactic penicillin and administration of pneumococcal vaccine is of primary importance in prevention of the overwhelming sepsis syndrome encountered in post-splenectomy patients.

Immunosuppressive therapy is a new area of investigation. Numerous agents have been reported in the past years helping to achieve varying successes. These agents are potent surpressors of both humoral and cellular function. Recent studies report the utilization of vincristine/vinblastine alone, or in conjunction with in-vitro treated platelets. Promising results in up to 60 per cent of resistant chronic patients has been reported.[22] Tempering these results is the recent negative report in children by the Seattle group.[23] The potency and side effects of these drugs render them a group not to be used without careful understanding and consideration.

The usage of varying types of transfusion in this disorder also merits discussion. Red cells should be given for anemia if bleeding has caused excessive losses. The use of plasma infusions to alter immunologic levels or yield a thrombopoietic factor has not been successful.[24] The use of plasmaphoresis to remove antibodies and increase platelet survival during complicated ITP has recently been reported and bears consideration in crisis situations.[25] Platelet transfusions rarely yield increments of platelets since they are destroyed rapidly in the body. They may result in a temperizing effect in bleeding while other therapy is emergent.[16]

Summary

ITP is a disease common in childhood and is associated with a good prognosis for spontaneous cure. It may go unnoticed in instances, be readily apparent in others, remit quickly, or in rare cases become chronic. Relapse may occur uncommonly up to ten years after original remission. A study reported in 1976 showed evidence that although remission is obtained, a definite antibody continues to circulate in children.[26] This makes the disease even more similar to the adult type. Research done in Israel by Mathoth showed children with ITP to have a significant learning disability as compared to a control group of children.[27] Thus Idiopathic Thrombocytopenic Purpura, even though usually clinically benign, can be of major significance. The consensus of proper therapy remains as yet unclear. The physician needs to be aware of this disorder and its ramification.

Acknowledgment

The author wishes to acknowledge the important contribution in research and technical aid made by: Mary Seals Singher.

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Rheumatology Corner

Juvenile Rheumatoid Arthritis

H. D. VENTERS, M.D. *

The etiology of juvenile rheumatoid arthritis (JRA) remains an enigma. Moreover long term observation is necessary for developing the prognosis. The clinical characteristics which allow a general classification of outcome are presented. Two aspects of this disease are of primary significance: First, the crucial diagnostic distinction between JRA and rheumatic fever, septic arthritis and acute leukemia; second, the potential perils of drug therapy. Supportive management, appropriate therapy, and attention to the psychological impact of this disease upon the patient and the family is also essential.

In a discerning paper in 1897, Still[1] noted the occurrence in children of a form of arthritis, distinct from that in adults. In general subsequent studies have supported this separation, although a recent presentation argued for a unified disease concept.[2]

Etiology

The etiology of juvenile rheumatoid arthritis (JRA) remains obscure.[3] Lee[4] in 1960 and others[5] have noted the resemblance of a syndrome following rubella to rheumatoid arthritis (RA). Deinard et al.[6] in 1974 presented data implicating rubella virus as a possible infectious agent, but subsequent investigators have been unable to confirm those findings.[7,8] Mycoplasma infection has been considered as a possible cause of human RA, but Cole[9] was unable to isolate this organism from the synovial tissue of patients with RA. He also found[10] no significant difference between the responses tested of 29 RA patients and 19 non-rheumatoid patients. Another intriguing infectious possibility is presented by Lyme arthritis.[11] Although originally described in Connecticut it was recently reported from Wisconsin.[12] Arthopods have been reported to transmit the causative agent.[13]

HLA typing potentially may further define the genetic role in the etiology of rheumatic disease.[14,15] In their review, Kemple and Bluestone[15] noted that 84% of the boys with spondylitis or sacroillitis and pauciarticular disease were positive for HLA-B27 in contrast to 8% of controls, although only 13% of patients with JRA were similarly positive against 8% of the controls. Mitsui et al.[16] found the HLA-B27 antigen in none of 27 patients with JRA. Nasrallah et al.[17] however noted a positive correlation between age of onset (12-24 years) especially in black males and B27 positivity. Sero-negative early onset patients may also include a separate sub-group as distinguished by the presence or absence of the B27 antigen. The association of HLA-B27 with late onset, male preponderance sacroiliitis and iridocyclitis has been noted by Schaller.[13]

Immunologic studies in JRA provide some new insights. As high as 40% of sero negative JRA patients may have "hidden" rheumatoid factor.[18] These patients may have a higher incidence of antinuclear antibodies. Patients with JRA may have a higher immunologic activity than controls.

Clinical Characteristics

Several series of large numbers of patients have been reported.[13,19-26] Tables 1 and 2 list the characteristics which serve to distinguish sub-groups. During the intervening years since Still's description various authors have emphasized findings during two distinct temporal aspects of the disease, i.e., those at onset, and long term.

At least three major, and probably two additional, sub types of JRA can be distinguished. A systemic onset with hyperpyrexia, typical rheumatoid rash, leukocytosis, anemia, hepatosplenomegaly, and pleuritis or pericarditis occurs in about one-fifth of the cases. Another one third of the children have a polyarticular form. In these cases females predominate, severe arthritis may be noted, and most are sero negative.

The third major type is represented by children with pauciarticular disease. Almost half of all patients with JRA may be so classified. Iridocyclitis is most commonly seen in this category. Girls are slightly more frequently represented in this group, and the boys tend to have ankylosing spondylitis.

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Differential Diagnosis

In patients with monarticular disease, the earliest possible exclusion of the diagnosis of pyarthrosis is critical. Pauciarticular onset may rarely be due to pyogenic disease. Rapid joint destruction occurs in untreated patients.[27] Precise bacteriologic diagnosis is imperative. Blood cultures in addition to joint fluid studies frequently improve the chance for organism identification.[28] Counter immune electrophoresis provides a rapid and reliable technique for bacteriologic studies of body fluids.[29]

The study of Dahl et al.[30] highlights some of the difficulties encountered in Minnesota regarding the diagnosis of rheumatic fever. Tables 1 and 2 of that paper are especially pertinent. Early, appropriate antibiotic prophylaxis is essential.

Acute leukemia in childhood may present with bone or joint involvement.[31] Initial hemograms and bone marrow examination may be normal and may not therefore rule out this disease.[32]

Systemic lupus, erythematous, scleroderma, polyarteritis, and dermatomyositis are other collagen diseases which may mimic JRA initially. Trauma is probably the most frequent cause of single joint pathology in children. Unfortunately, because a history of injury is so common in this age group JRA is not considered. However, about 10% of patients with JRA have significant antecedent trauma.

Cervical Spine

While more commonly occurring in adults[32-35] cervical spine involvement has been reported during the course of JRA.[19,21-26] Kiprova et al.[36] noted that this occurred in 52% of children with disease onset prior to age seven years compared with only 20% who had the onset after age seven. Spontaneous axial subluxation may rarely be the presenting problem in JRA.[37] Radiologic examination of the cervical spine including flexion and extension studies are suggested when clinical signs, including pain on neck motion, are

TABLE 1

Clinical Characteristics of JRA
Noted as Percentage of Cases with Positive Findings

Author	N	F/M	RASH	CERVICAL SPINE	NODULES
Ansell & Bywaters[22]	316	196/120	25% overall	66% overall	7% overall assoc. with high R. F.
Barry & Stillman[26]	200	149/51	42% with systemic onset	systemic 56% poly 46%* pauci 20%†	20% overall, 36% of pts. with polyartic onset
Bianco & Peterson[25]	163	114/49	more common in males	instability rare	—
Brewer[23]	100	61/39	4% overall	fusion late	10% assoc. with + R.F. Histology: 1. may mimic rheumatic fever 2. fibrosis common
Coss & Boots[19]	56	44/12	—	13% overall	4% overall
Grokoest[21]	110	78/32	9% overall	28% overall bony ankylosis of post. elements of cerv. spine pathognomonic	2% overall
Schaller & Wedgwood[24]	124	86/38	systemic 94 poly 0 pauci 0	systemic 0 poly 50%	11% overall
Schaller[13]	112	71/41			
systemic		10/12	95%		0%
poly RF —		24/2	0		4%
poly RF +		7/1	0	more common	88%
Pauci chr. iridocyclitis		11/4	0		
Pauci ♀		18/0	0	occas.	
Pauci ♂		0/18	0		
Ankl. Spond.		1/4	0		
Johnson & Dodd[20]		21	70%		

*Poly > 5 joints
†Pauci < 5 joints

observed. Surgical fusion may be necessary for correction of the unstable cervical spine as well as for prevention of serious neurologic sequelae.[38,39]

Treatment

As noted above physical therapy plays a major role in the management of JRA. Rest therapy in RA has advocates as well as antagonists and deserves ongoing evaluation, with the inclusion of JRA patients.[40–42]

Salicylate therapy has also held an important role in the treatment of JRA. Recent studies have pointed to the occurrence of hepatotoxicity occurring in JRA patients.[43,44] However other authors noted that hepatic dysfunction is also seen as a primary part of JRA and SLE.[45–47] Athreya et al.[48] suggest discontinuing salicylate therapy only in these children who develop bleeding. Frequent monitoring of liver function and salicylate levels are indicated.[49]

The Pediatric Rheumatology Collaberative Study Group[50] reported that in comparison with aspirin, therapy with tolmetin sodium resulted in less frequent transaminase elevations. Equal analgesic and anti-inflammatory effects were observed.

Manipulation of the immune system has also been attempted. Recently Hoyerall et al.[51] were unable to demonstrate significant theraputic effect of the use of transfer factor.

The anemia associated with JRA has been considered refractory to iron therapy. Serum ferritin levels correlate reasonably well with disease activity.[52] Koerper et al.[53] using oral ferrous sulfate in a dose of 2-3 mg/Kg/day noted a hemoglobin rise in some of

TABLE 2

Clinical Characteristics of JRA
Noted as Percentage of Cases with Positive Findings

Ref.	Rheumatoid Factor/ANA	Iridocyclitis	Onset	Prognosis
2	13 overall	chronic — 4% unilat. 2%	Dx: > 4 joints > 3 mo. or + biopsy	50% no residual at 5 years
26	systemic 11% poly 38% pauci 13%	18% (uveitis)	systemic 18% poly 41% pauci 41% 73% > 10 yrs. age	Uveitis
25		—	systemic 10% No poly, systemic 60%, poly with systemic 30%	disability at 5 yrs. = in poly & mono
23	40%	—	systemic poly/ pauci 44%, poly No systemic 56%	severe disease mono — good
19	N. A.	—	adenopathy 60% pain 100%	Duration: 42% > 5 yrs. 24% > 7 yrs.
21	10%	2%	pain free 27% poly 58% mono 39% → poly In 65% of these	hyperhydrosis growth disturbance 47%
24	systemic 0 poly 13% pauci 2%	systemic 0 poly 11 pauci 26	systemic 26% poly 37% RF +, pauci 37%	severe 33% severe 33% severe 0
13	systemic 0/0		mean age 5.7 yrs. fever 100% hepato/ splenomeg. –86%	32% serious disability
	poly RF-0/23%		mean age 5.1 yrs. lg. & small joints — 80%	15% serious disability
	poly RF + 100%/75%		mean age 11 yrs. progressive disease	50% serious disability
	(Pauci) chr. irid. 0/67%	100%	pauci-mean age 2.5 yrs.	mild arthritis 33% blind, one or both eyes
	pauci 0/39%		pauci mean age 4.3 yrs.	0 serious disability 94% do well on ASA
	pauci 0/0		mean age 10.2 yrs. hip — 33%	44% sacroiliitis 78% do well
	ankl; spond 0/0	20% acute	mean age 8.8 yrs. ankl spond. later	100% cont. active dis.

these patients suggesting the existence of iron deficiency.

Chronic pain may be erroneously overlooked. Evaluation of the impact and degree of pain may be difficult.[54] Explanation of the role of therapy for anti-inflammatory as well as analgesic effects should be stressed.

Summary

JRA is a disease of unknown etiology whose characteristics and course differ somewhat from adult onset RA. Early differential considerations especially for septic arthritis, rheumatic fever, and acute leukemia are mandatory. Certain features of the mode of onset, laboratory evaluations, and progression of the disease may be of help in establishing the prognosis. Management may require a variety of drugs, but physiotherapy and salicylates remain the primary therapeutic modalities. Drug toxicity may occur and should be anticipated.

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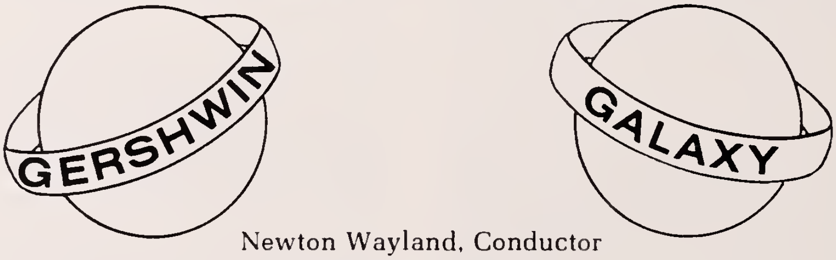

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Army Reserve 470
Beltone Electronics Corp. 394
Burroughs-Wellcome Co. 436
Classified Advertising 467
Finley & Friday, Inc. 448
Health Central 386
Hempel Financial Corporation 462
Lilly, Eli & Co. 388
Loma Linda Foods 396
Mead Johnson Pharmaceutical Division 439, 440, 441, 442
Medcalf Orthopedic Appliance Co. 472
Medical Protective Company 462
Merrell-National, Inc. 420, 421, 452, 453, 454
Merck Sharp Dohme 386
Minnesota Medical Association Auxiliary 468
North Central Medical Conference 410
Pharmaceutical Manufacturers 460, 461
Purepac 459
Roche Laboratories .... Cover 2, Cover 3, 4
Smith, Kline & French 451
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Upjohn Company 422
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(Continued from Page 469)

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(Continued to Page 472)

(Continued from Page 471)

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Contraindications: Tablets in children under 6 months of age; known hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Withdrawal symptoms (similar to those with barbiturates, alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals (drug addicts or alcoholics) under careful surveillance because of predisposition to habituation/dependence.

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

ORAL: Advise patients against simultaneous ingestion of alcohol and other CNS depressants.

Not of value in treatment of psychotic patients; should not be employed in lieu of appropriate treatment. When using oral form adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may be associated with temporary increase in frequency and/or severity of seizures.

INJECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist, use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs.

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms (similar to those with barbiturates, alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal/muscle cramps, vomiting, sweating). Keep addiction-prone individuals under careful surveillance because of predisposition to habituation/dependence. Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors and antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Limit oral dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

Supplied: Tablets, 2 mg, 5 mg and 10 mg, bottles of 100 and 500; Tel-E-Dose® (unit dose) packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Ampuls, 2 ml, boxes of 10. Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam, compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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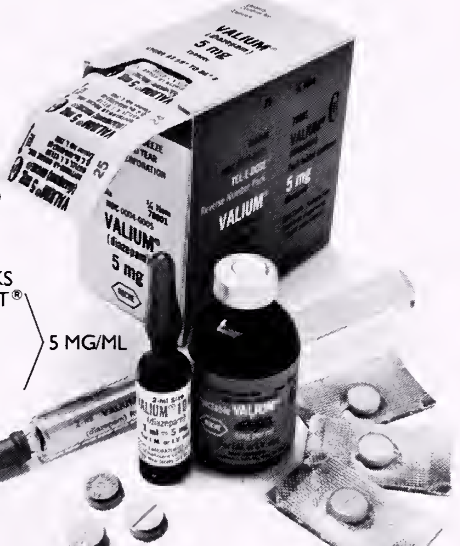

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Medical Oncology Special Issue
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Valium (diazepam/Roche) is a benzodiazepine with a character all its own. Pharmacologically, it is a potent skeletal muscle relaxant and anticonvulsant (in adjunctive use), as well as an antianxiety agent. Pharmacokinetically, only Valium provides active *diazepam* as well as the active metabolites 3-hydroxydiazepam, desmethyldiazepam and oxazepam.

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Another important aspect of the clinical character of Valium is safety. Though drowsiness, ataxia and fatigue are possible, these and more serious side effects are rarely a problem. Of course, as with all CNS-acting drugs, patients taking Valium should be cautioned against driving, operating dangerous machinery or the simultaneous ingestion of alcohol.

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The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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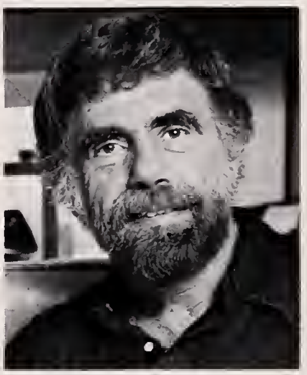

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Contents — July, 1979

Volume 62:7
Pages 473-564

COVER PHOTOGRAPH — "Dandelion Seeds in the Sunset"
R. Hamilton Smith 488

PRESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association 477

EDITOR'S NOTEBOOK — How to Avoid Running: or, Time-Consuming Exercises for Non-Runners — *Richard L. Reece, M.D., Editor-In-Chief* 479

MESSAGES IN ONCOLOGY

Introduction

Control and Cure of Cancer —
B. J. Kennedy, M.D., Guest Editor 487

Detection: Techniques in Cancer Diagnosis

Use of Imaging Techniques in Cancer Diagnosis —
Samuel Feinberg, M.D. 489
Role of Nuclear Medicine in Oncology
Merle K. Loken, M.D. and Mathis P. Frick, M.D. 491
Role of Gastrointestinal Endoscopy and Peritoneoscopy in Diagnosis of Cancer — *I. Dodd Wilson, M.D.* 494

Biologic Markers in Cancer Diagnosis and Monitoring

Estrogen Receptors in Breast Cancer
David T. Kiang, M.D. 497
B & T Markers in Leukemia and Lymphoma
Clara D. Bloomfield, M.D. 499
Chorionic Gonadotrophin and Alpha-Fetoprotein Markers for Testis Cancer
George Bosl, M.D. 507

Adjuvant Chemotherapy

Breast Cancer — *B. J. Kennedy, M.D.* 509
Large Bowel Cancer — *Theodor B. Grage, M.D.* 511
Ewing's Sarcoma — *Mark E. Nesbit, Jr., M.D.* 513
Malignant Melanoma — *Gerald J. Vosika, M.D.* 515

Progress in Therapy of Advanced Cancers

Lung Cancer — *Gerald Vosika, M.D.* 519
Breast Cancer — *David T. Kiang, M.D.* 521
Testis Cancer — *B. J. Kennedy, M.D.* 523
Ovarian Cancer — *B.J. Kennedy, M.D.* 525
Acute Lymphoblastic Leukemia of Childhood
Peter F. Coccia, M.D. and Mark E. Nesbit, Jr., M.D. 527
Acute Non-Lymphocytic Leukemia — *Clara D. Bloomfield, M.D.* 529
Acute Non-Lymphocytic Leukemia in Elderly Patients
Bruce A. Peterson, M.D. 531
Non-Hodgkin's Malignant Lymphoma — *Clara D. Bloomfield, M.D.* 533
Investigational New Drugs in Cancer Chemotherapy
Bruce A. Peterson, M.D. and Kathleen Briscoe, M.D. 536

Complications in Cancer Management

Opportunistic Infections in Patients with Cancer
Bruce A. Peterson, M.D. 539
Hypercalcemia in Neoplastic Diseases — *Daniel H. Frenning, M.D.* 541
Intravascular Coagulation — *G. J. Bosl, M.D. and J. R. Edson, M.D.* 544

Topics in Cancer

Nutritional Management during Cancer Therapy
Athanasios Theologides, M.D. 547
Immunotherapy in Cancer — *Gerald Vosika, M.D.* 549
HEUMATOLOGY CORNER — Malignant Disease and Rheumatism
Richard H. Ferguson, M.D. 551

EALTH CARE COST COMMISSION

Richard J. Frey, M.D., Chairman 553
Physicians Act on Cost Commission Report 555
INNPAC HELPS YOUR PRACTICE OF MEDICINE
L. Ashley Whitesell, Jr., M.D. 508
ONTINUING MEDICAL EDUCATION 496, 498, 532, 552
LASSIFIED ADVERTISING 561
NDEX TO ADVERTISERS 554

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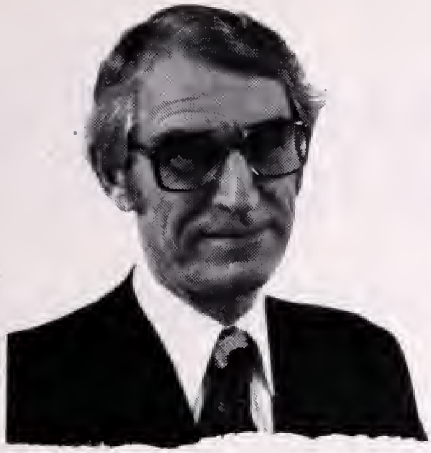

President's Letter

At a time in the past within the recollection of many, July brought with it marching bands, parades, and political oratory with patriotic overtones in celebration of Independence Day. July 4th seemed a happy day set aside to recognize a feeling for our country. Patriotism today is out of vogue and considered chauvanistic. But regardless of the name we apply there is still a need for citizens to be concerned and actively working to improve our society. Physicians are citizens with very special knowledge about the problems of illness and health maintenance. They can offer an expert opinion about what constitutes quality medical care and what it should cost. They have worthwhile thoughts about such things as patient access to health care, physician distribution, and hospital placement and capability.

I believe that society wants to hear the ideas of physicians, but is not equipped to process individual opinion. Only through organized medicine will we have an audience with health planners and politicians, and our voice then will carry weight in direct proportion to the strength of the organization in terms of the percentage of eligible physicians who are members. I have a strong conviction, therefore, that all physicians have a citizen's duty to be dues paying members of organized medicine at the county, state and national level. Even more they have a duty to be active in pouring their thoughts and ideas into the organization for distillation and refinement, and once those ideas are considered and accepted, modified, or discarded they must allow medicine to express with a single voice the opinion of the majority.

July is a month when the majority of new physicians come into practice. Most will join an already established physician or group of physicians. I would, therefore, encourage those already in practice to seriously consider paying the dues (county, state, and AMA) as a legitimate office expense for any new member joining them. I would then further ask that the established physician personally acquaint his new associate with the organizational structure and operation of the medical society. To bring him/her to the House of Delegates and Reference Committee meetings at the next annual gathering of the MMA would be most helpful in stimulating excitement and interest.

I ask your help in bringing new graduates into the activity of organized medicine as soon as possible.

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

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Editor's Notebook

How to Avoid Running: or, Time-Consuming Exercises for Non-Runners

"Avoid running at all times."
Satchel Paige

"Exercise is one of the most provocative words of our time. Many praise exercise as a vital-even joyful part of their lives. Others register dismay and describe guilt feelings when confronted by the word."
Harvard Medical School
Health Letter, February, 1976

Psst. Pssst! Psssssst!!

You. Yes, you. All you non-runners out there. You can come out of the closet now. This essay is for you.

And why shouldn't it be? After all, who else speaks for you? Oh, William Buckley has devoted a single tongue-in-cheek column to non-jogging.[1] And two non-runners have written a satirical book "The Non-Runner's Book."[2] But no one takes you seriously.

Serious Mistake

Which is a serious mistake. You make up the largest silent majority in America. There are 200 million of you, compared to 25 to 30 million runners. Think of your political power. Why, you could run for anything and win. So why run at all? That is precisely the point. You don't have to run, and you don't have to apologize for not running.

Stop Running Yourself Down

Yet, many of you run yourselves down because you don't run. You're guilty about not running. Why? Because runners tell you they feel good, look good, work better, perform better, have improved self-images, are going to live longer, and at certain moments — breaking through "a wall of pain" or getting a second wind — achieve transcendental bliss.[3]

These walleyed and windy arguments have weakened your will not to run. You are beginning to say: Hey, maybe these guys have something. You have started to think: Maybe I should tone up my cardiovascular system and rev up my anaerobic metabolism, so I can have a resting pulse of less than 50. You are telling yourself: Maybe if I whip myself into shape I can perform feats fit only for an 18-year-old.

Your True Desires

But deep down, you don't buy these arguments. You really don't want to run. You loathe exercise, except for sleeping, resting, and perhaps walking. In the long run, you know everyone will die anyway. So why suffer while waiting in line for the inevitable? Still, runners keep jogging your guilt complex. So, even though you don't want to run, you need rational excuses — legitimate time-consuming activities — that will leave you no time to run.

Six "Exercises"

You crave, in short, something that will help you avoid running at all times. Below I describe six "exercises" (I thought the word "exercises" would make you feel better about not running) whereby you can avoid running by consuming time doing something else. Most of these "exercises" are strictly mental. You don't have to leave your bed or chair to carry them out. A few require minor physical activity, none of which produces a sustained pulse rate of over 75.

Exercise One — The Newspaper Nuance, A Political Ploy

"I'm not running."
Senator Edward Kennedy
***Boston Globe*, June 19, 1979**

For your first exercise, stay in bed and read your daily newspaper. The daily newspaper, you see, is a fine source of nonrunning inspiration. Newspapers contain news about politicians. Politicians have mastered the nonrunning art. General Sherman, bless his soul, started it when he informed a reporter: "If nominated, I will not run." Calvin Coolidge, a laconic New Englander, carried on the tradition when he declared: "I choose not to run."

Another New Englander, Senator and Ex-Officio President, Edward Kennedy, now ranks as our most superb nonrunner. Indeed, he has developed nonrunning to a high art. The more he says he is not running, the stronger he gets. There's a chance he will become President without running at all.

President Carter, on the other foot, is definitely running. We are reliably informed he runs 30 minutes to one hour each day, has lost from 155 to 147 pounds, and has dropped his resting pulse from 70 to 50. At 50, there are signs he may be having difficulty perfusing his brain adequately. At any rate, according to the polls, Carter is running downhill and may soon run out of gas.

Have you stopped to think that maybe the game of politics is like the game of life? While your friends, are off running (or is it running off?), steadily running down and losing momentum, you are storing energy and getting stronger every day. Spend at least an hour a day reading newspapers to gather information on nonrunning techniques. And remember: an hour a day keeps athlete's feats away.

Exercise Two — The Roadrunner's Ruse, A Hazardous Hamper

"Last year motorists struck and killed 125 joggers in New York City and suburbs."
***New York Times*, Spring, 1979**

To hamper your desire to run, think of possible roadrunning hazards. You have, no doubt, seen Roadrunner cartoons: A lone bird streaks across desert roads, exposing himself to innumerable hazards, yet never gets hurt. Running is not like that. Running is hazardous. Runners are slow-moving targets for fast-moving cars driven by angry motorists, who resent runners clogging and congesting *their* roads. Runners are also inviting bait for dogs. Then, too, runners must battle rain, sleet, snow, fog, smog, wind, darkness, twilight, glare, cold, and heat. Heat stroke does in more runners than all other elements combined.

But not all hazards lie on hot roads. Some lie in cold beds. By arising at the crack of dawn, runners often cool off warm spouses. You would not do this. As a nonrunner, you know the beneficial effects of one-half hour's exercise before breakfast are more than offset by the mental wear and tear of getting out of bed early. Running around at night is not likely to make spouses feel any warmer. Lastly, runners must cope with jealous nonexercising peers, who do not take kindly to streaking striders, bounding bounders, or jaunty joggers clad in modish towel suits and stylish sneakers.

Exercise Three — The Mathematical Maneuver, A Pounding Problem

"Today my heart beat 103,389 times, my blood traveled 168,000 miles, I breathed 23,040 times, I inhaled 428 cubic feet of air, I spoke 4,800 words, moved 750 major muscles, and I exercised 7,000,000 brain cells. I'm tired."

Bob Hope, *Reader's Digest*, January 1949

Have you given serious thought to the pounding your body would take when you are running? Well, lie on your bed, sit at your desk, and think about it. Do it before you do something footish. Suppose you weigh 200 pounds, to take a nice round figure. And you want to get in good enough shape to run a mile in eight minutes at an average pulse rate of 120 and a respiratory rate of 30 a minute. Now calculate the toll on your feet, your heart, your lungs, and your bones, joints, and ligaments. My seat of the pants' estimates are: you will lift and drop 110 tons of flesh and bone on your calloused soles, pump 150 liters of blood with your hardworking heart, and exchange 800 liters of air with your laboring lungs.

For devastatingly detailed discussions at the damage from pounding on your musculoskeletal system, consult Sheehan's "Medical Advice for Runners"[4] and the June 1979 issue of *Emergency Medicine.*[5].

If you are merely feeling listless, and want to run over a list until the urge to run fades, look at the list below, which an orthopedic group in St. Paul compiled:[6]

"*The canvus foot* or high arch foot produces a large number of injuries related to the foot, leg and thigh. *External* rotation pain is noted at the hip. *Iliotibial band pain* at the lateral aspect of the knee. This is the most recalcitrant problem, causing an average of three months off running.

"*Plantar fasciitis* is a problem which comes from the tight plantar fascia.

"The *pronated* foot or flat foot produces more injuries numerically, but less time off. The average time off running for a pronation related injury is *six weeks*. *Adductor strains* can be seen due to internal rotation of the entire extremity.

"*Sciatic nerve irritation* can also be related to excessive rotation of the extremity secondary to pronation.

"*Chondromalacia patellae* is the most common pronation related problem and is generally seen as pain on the medial facet of the patella. "*Shin splints*", although actually three or four different entities, seem to have some basis in pronation. *Achilles tendonitis* is definitely related to pronation because of selectively tight heel cords.

"*Stress fractures* of the metatarsals are most often related to pronation. They require six weeks before return to running."

Exercise Four — The WOE (Weight of Evidence) Index, An Exhaustive Exercise

"The marathon is a 26-mile 385 yard (42.195 km) running race that taxes the participant to the extreme. By virtue of this fact, the marathoner's body and mind must be conditioned to an exceptional degree to prepare, endure, and master this race. The human discipline brought to bear in this endeavor has medical, physiological, and psychological consequences."

Paul Milvy, in his introduction to, "The Marathon: Physiological, Medical, Epidemiological, and Psychological Studies," A single volume of the *Ann NY Aca Scien*
301:1-1090, 1977, which weighs 1247 grams (2.8 pounds)

I am assuming most readers of this piece are physicians — men and women of science. You don't simply jump on the latest medical bandwagon and run off in all directions. You study and weigh the evidence to see what's afoot. You read the medical literature — all of it. After all, that is where all the facts are; and that's where you can run around in academic circles. Besides, reading the medical literature consumes enormous amounts of time and physical effort.

Time? Yes, time. Let's say you want to read the medical literature for the last ten years on jogging and running. To find that literature, you will turn to the *Index Medicus*. There you will find, under "Exertion" and "Running", everything you ever wanted to know about benefits and complications of physical exertion. Since 1970, these numbers of articles on exertion and running have appeared: 1970 (560 articles), 1971 (700 articles), 1972 (910 articles), 1973 (770 articles), 1974 (820 articles), 1975 (800 articles), 1976 (795 articles) 1977 (885 articles), and 1978 (940 articles). If you take 15 minutes to find and read each article, it will take 1793 hours, or nearly 75 solid days, to complete the reading. This marathon reading will make you well-informed (a true scientist always reads exhaustively), and you will be rewarded with titillating tidbits of information e.g.: Did you know that among 4300 starters in the 1977 Mayor Daley Marathon in Chicago, 20 runners came down with jogger's nipples? Or that one dashing 53-year-old circumcised physician suffered penile frostbite (''Pathogenesis of the syndrome was assessed as tissue response to high air velocity at −8° C, penetrating the interstices of polyester double-knit trouser fabric and continuing through anterior opening of Dacron-cotton undershorts, impacting upon receptor organ to produce the changes described'').[7]

Physical effort? Yes, physical effort. If you systematically plow through the *Index Medicus* for the last 10 years, you will lift volumes weighing nearly 300 kilograms, or 660 pounds (figure).[8] The 1978 *Index* alone weighed 75 pounds.

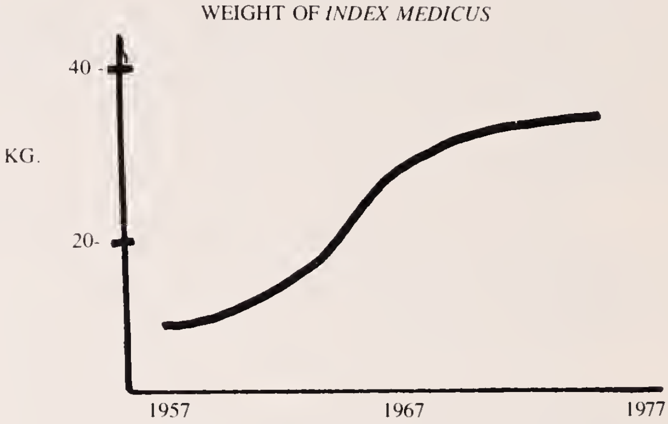

Figure — Weight of *Index Medicus*, 1957-1977.

If you review the literature over the last ten years, lifting all volumes, taking all journals off the shelves and reading all material, you will find the weight of evidence is overwhelming. You will consume so many footpounds of energy you will be too tired to trot.

Exercise Five — The Jogger's Jog, Two Quickening Queries

> *''If jogging is defined as an activity representing a stage between walking (in which the body is always supported on one foot) and running (in which both feet are clear of the ground for extended periods), one can postulate that the exertion of jogging is slightly more than that of walking and slightly less than that of running.''*
>
> **Allan J. Ryan, M.D.**
> ''Which is more helpful for cardiovascular conditioning jogging or running?''
> **JAMA. 238-165, 1977**

Among definitions of ''jog'' are: (1) to give a slight shake or push: nudge, (2) to rouse to alertness, (3) to cause to go at a jog, (4) to move up and down or about with a short heavy motion, (5) to run or ride at a slow trot, (6) to go at a slow, leisurely, or monotonous pace: trudge.

The purpose of this exercise, The Jogger's Jog, is to quicken the jogger's pride, pulse, and patter by asking leading questions. Once a jogger begins to talk, he will run on and on. You can then sit back and relax.

EDITOR'S NOTEBOOK

"Are you a jogger or a runner?" or "Why do you run?" are excellent queries. These are not idle questions. For you are striving to find if your conversational target has his feet on the ground. Joggers will tell you they run for fun and fitness, but you know they have a secret passion for fashion.

Let's face it. Running and the "discipline of running" are "in," and idle jogging is "out." This year's New York Marathon, to be held in October, 1979, has already attracted 21,000 entries and only 14,000 can run. Runners all over the world are coming, and many are chartering 747s to make the trip.

Here, for your use in bantering with joggers, are "in" terms to drop. Joggers' passions you will note, extend to other fashions. These buzz words worked into any conversation are good for at least a few minutes of trendy running commentary and may even call for a marathon discussion.

"out:" words or phrases	corresponding "in" words or phrases
1. moderation	1. deprivation
2. exercise	2. discipline
3. aspirin	3. transcendence
4. coke	4. Perrier
5. valium	5. vitamins
6. marathon dancing	6. marathon running
7. marriage licenses	7. cohabitation contracts
8. three martini lunches	8. no lunch
9. meat and potatoes	9. sprouts and spinach
10. earth shoes	10. Denver boot
11. Sports Illustrated	11. Runners's World
12. Saving yourself for your husband	12. Saving yourself from your husband
13. golf	13. racquetball
14. ballet	14. aerobic dancing
15. republicans	15. Neo-conservatives
16. jocks	16. world class athletes
17. jogging	17. Marathon running*
18. oil	19. nuclear
19. nuclear	19. coal
20. coal	20. solar
21. solar	21. wood
22. wood	22. hypothermia

---

*Especially status-ridden if you mention you have flown off to participate in such "in" races as Chicago's Daley Race, Honolulu Marathon, New York Marathon, and Boston Marathon.

It is also good form and talk inciting to ask how many miles a week runners run. Then you can level with them about their true status:

- Level 1 — fitness jogger — 9 to 20 miles
- Level 2 — recreational runner, 20 to 40 miles
- Level 3 — competitive — 40 to 80 miles
- Level 4 — world competitor — 80 to 100 plus miles

A word of caution. You can jog joggers, but you can't josh them. Running is a serious business, as you can plainly see from downcast looks on runners' faces. You may have misinterpreted these pained facial expressions as boredom. It is not boredom. It is dogged dedication.

Here is how Bill Rodgers, winner of the Boston Marathon, explains the seriousness of running: "Whatever the rationale folks use to begin running, I think that in time these reasons become secondary to a more dominant force: running becomes an addiction, an integral part of one's attitude and life style."[10]

This grim attitude has led Lewis Thomas to observe: "Jogging is done by swarms of people, out onto the streets each day in underpants, moving in a stolid sort of rapid trudge, hoping by this to stay alive."[11]

Exercise Six — The Warm-up Wedge, A Finishing Kick

"Wedge – the simplest tool known to man."
Anonymous definition

If all previous gambits fail, you may want to resort to the simplest ploy of them all, the warm-up wedge, to avoid running. Experts on exercise agree: (1) all exercise should be preceded by a warm-up period; (2) for exercise to be effective, you should engage in some form of sustained exercise at least three times a week.

The Warm-up Wedge is simple to understand. If you *must* exercise, simply wedge in other, less strenuous exercises, before you jog. "Warm-up" to jogging by participating in these exercises in this order, a week at a time.

Exercise	Exertion Rating*
Bowling	51
Softball	64
Go (cart)	66
Walking	102
Calisthenics	126
Tennis	128
Skiing (alpine)	134
Basketball	134
Skiing (alpine)	139
Handball/squash	140
Skating	140
Swimming	140
Bicycling	142
Jogging	148

---

*As established by President's Council on Physical Fitness and Sports from evaluations and ratings of seven experts. Each exercise was rated on scale or zero to three for heat and lung endurance, muscular strength, flexibility, balance, and general well-being.[12]

By the time you get to jogging, you won't have to, which is just fine, because you didn't want to.

Final Rundown

To avoid running at all times, stay in your bed and read about political non-runners; gaze at the ceiling and consider all the hazards of running; relax and calculate the pounding running will impose on your body; sit in your chair and scour the medical literature for everything you can find on physical exertion; and, finally, once all these essentially nonphysical ploys are exhausted, warm up gradually for running by pursuing every possible less strenuous physical activity. In short do everything but run. Above all else, take pride in your non-running status. Stand up, sit down or roll over and be counted.

Richard L Reece MD

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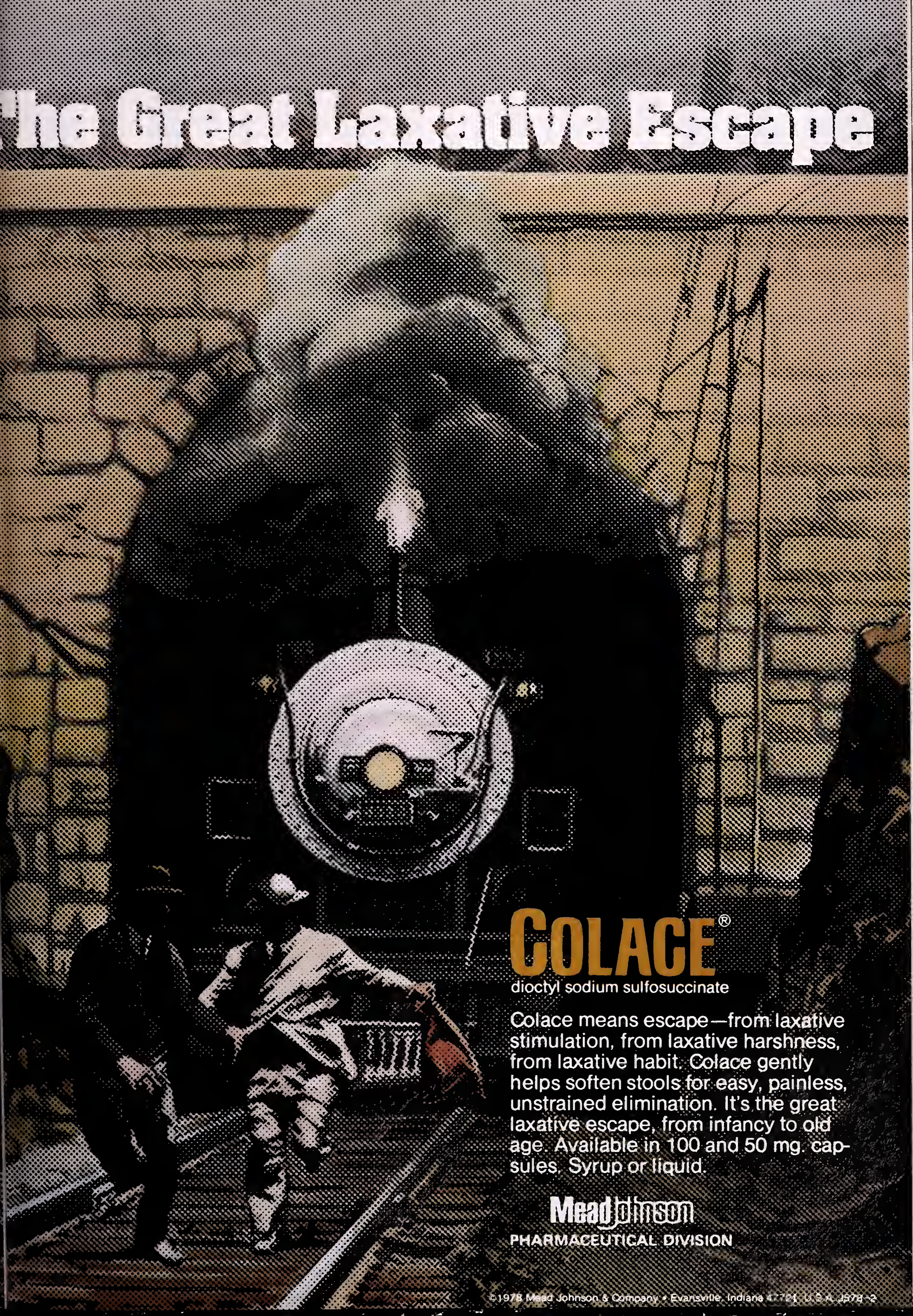

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Control and Cure of Cancer

B. J. KENNEDY, M.D.*
Guest Editor

THE PROGRESS in oncology in the fields of Medical Oncology, Surgical Oncology, Pediatric Oncology and Therapeutic Radiology has progressed to the point that some cancers can be realistically controlled and even cured. The mortality from cancer of the cervix has decreased remarkedly in the past 40 years, acute leukemia in children appears to be cured in over 50% of the affected children, and a variety of other tumors are cured by surgery, radiotherapy, chemotherapy or combinations of these therapeutic modalities. Such progress requires the practicing physician to be cognizant of the recent therapeutic concepts in order to provide his patients the most effective, modern methods of management of their cancer.

This issue of MINNESOTA MEDICINE devoted to *Messages in Oncology* is an attempt to emphasize the progress made in specific areas of cancer management. These brief messages provide a rapid retrieval capability and a resource for the physician to return to for information that requires repeated attention.

Medical Oncology represents a new sub-specialty of Internal Medicine that has had outstanding growth during the past six years[1]. Of the nine sub-specialties of Internal Medicine, Medical Oncology is now the fourth largest in terms of the number of physicians certified in this new sub-specialty. This increase in manpower is the result of the need to meet the demands to care for patients with the new modalities of chemotherapy and coordinate the management of adult patients with cancer. Pediatric Oncologists have already provided notable strides in controlling and curing cancer in children.

From the original cell, cancer undergoes doubling to increase its volume. Approximately 25 doublings are required to attain a tumor size of more than 1 cm., the level at which clinical detection becomes possible. Five more doublings result in a tumor size comparable to that of a football. It is obvious that the physician in dealing with measurable cancer is already dealing with a moderately advanced disease and little time remains for him to carry out treatments that can be curative.

Emphasis on prevention (e.g. avoidance of carcinogens) is an important aspect of routine medical care. Almost 50% of deaths from cancer in males could be avoided if cigarette smoking was eliminated. The office practice of medicine can emphasize early cancer detection by routine screening measures and awareness by the physician of those diseases that can be detected early in patients at high risk. New techniques in radiology and nuclear medicine provide new opportunities to increase the chances for early detection of cancer.

Once cancer is detected, the management of the disease is dependent upon the stage of disease at time of detection. To aid the physician in managing patients with cancer and to establish reliable methods of reporting cancer data, staging systems for defining the extent of the disease have been established. These are employed at the time of the initial detection of the cancer. The American Joint Committee for Cancer Staging and End Results Reporting provides a manual for the various tumor staging systems[2]. The physician is urged to be familiar with these and apply them regularly.

The initial definitive treatment of early detected cancer emphasizes surgery, radiotherapy, and adjuvant chemotherapy. The efforts to detect cancer earlier have improved the capabilities of surgery to cure cancer (breast, testis, colon, osteogenic sarcoma). In some, these results are augmented by the addition of adjuvant chemotherapy Radiotherapy continues to provide a curative role in other cancers (larynx, skin, Hodgkin's Disease, seminoma of the testis). With combinations of these therapies, others are cured (cervix, Wilm's tumor, endometrium, ovary, head and neck). More recently, hormonal and chemotherapies have not only been able to control cancer, but are curative in some advanced diseases (e.g. testis cancer, histiocytic lymphoma, choriocarcinoma of the endometrium, Burkitt's lymphoma). Failure to control cancer is still a major problem in the cancers of the esophagus, stomach, pancreas, lung, brain, and those tumors detected in late stages.

A notable advance in the early detection and monitoring of cancer following definitive therapy has been attained in the development of biologic markers, These tests provide a means for early detection as well as monitoring the disease following definitive therapy, searching for evidence of recurrence or reactivation of the disease. For example, the acid phosphatase in prostate cancer, paraproteins in multiple myeloma, alphafetoprotein and beta subunit of human chorionic gonadotrophin in testis cancer, and carcinoembryonic antigen in colon cancer. Biologic markers determined on tumor tissue have provided further guidance as to the biologic nature of breast cancer (e.g. estrogen and progesterone receptors). These determinations become increasingly manditory in the initial management of cancer as well as during the course of the disease.

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Remarkable advances have been made in the hormonal therapy or chemical therapy of advanced malignant disease. These therapies were originally employed as palliative treatments. Later, it was apparent that long-term control of cancer could be attained. Now, cure of advanced disease is recognized as a realistic accomplishment.

In the development of this new field of medicine, definitions of tumor response have been clarified. Subjective improvement or stabilization of the disease is important to the patient and does result in prolongation of survival. Partial regression of tumors implies greater than 50% shrinkage of measurable tumor with no evidence of progression. Complete regression of cancer implies disappearance of all measurable disease by even the most vigorous attempts at detection. It is the complete regression category that is of most significance in attaining cure of the disease.

Eventually in the course of cancer that has not been cured, there comes a phase in the life of a patient in which no definitive treatment is available and yet considerable support is necessary. The appropriate use of analgesics, palliative radiotherapy or surgery, and non-specific chemical therapy can provide a comfortable life for the patient. Frequently, the term "terminal" is employed in describing such patients. The use of this term is to be deplored and should not be part of the physician's vocabulary for living patients[3]. During the phase of dying from the disease, the patient needs support from the physician, family, and supporting health personnel.

In coping with cancer, it has been demonstrated that group counseling is an effective support mechanism for patients and their families[4]. This important area requires the participation of the clergy, nurses, social workers, occupational therapists, dieticians, and the physicians.

The brief *Messages in Oncology* in this issue cannot encompass all the progress within each specific tumor category. Some statements may appear to be dogmatic. Documentation of the statements made will be provided by the individual authors on request of the reader.

By the physician's awareness of the progress in oncology in terms of prevention, early detection, and definitive therapy, control and cure of many cancers is a reasonable accomplishment.

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COVER PHOTOGRAPH

"Dandelion Seeds in the Sunset"

R. Hamilton Smith, a free lance photographer, took the cover photograph on the Mississippi West bank, in Inver Grove Heights, in late summer. He is well known for his technique of catching the unusual with his camera.

Mr. Smith shows his collections, one of which is called "Earth Imagery," around the country, and this year, he had a showing at the Bell Museum of Natural History at the University of Minnesota. In addition, he conducts workshops periodically at the Hennepin County Library.

He has had work published in *National Geographics, Mariah, Nature Conservancy, Minnesota Volunteer* and the Sierra Club calendars.

Presently, Mr. Smith is on a canoe trip to the Canadian Artic "catching the unusual" with his camera for future shows.

Use of Imaging Techniques in Cancer Diagnosis

SAMUEL FEINBERG, M.D.*

NEW RADIOGRAPHIC techniques provide means of improved cancer diagnosis and better means to evaluate treatment results. Of particular value are mammography, chest tomography, ultra-sound and computerized tomography.

Mammography

The use of mammography for diagnosis of breast cancer should be individualized. Routine mammography is not indicated in all patients. In patients at high risk of developing breast cancer, mammography is indicated. These include a family history of breast cancer, nulliparous patients, late pregnancy, early onset of menstration, and late menopause. Personal histories of cancer in the breast necessitates examination of the opposite breast. Patients who have had a personal history of endometrial cancer also are included in the mammographic program.

In the initial health examination of patients over the age of fifty, xero mammography is indicated in order to classify the patient's breast either as being abnormal or falling into one of the categories described by Wolfe, which would indicate whether follow-up mammograms are necessary.

Regardless of age, nipple discharge, lumps or thickenings in either breast due to mammary dysplasia are an indication for xero mammography. From the point of view of those who have had mammography, those who have had evidence for mammary dysplasia or prominent ductal pattern as enumerated by the Wolfe classification are included for periodic follow-ups.

Chest Tomography

Chest tomography is employed according to the patient's diagnosis and routine chest findings. Depending upon the primary, lung tomography is indicated in patients who have a potential for pulmonary metastasis. In such cases, full lung tomography looks for metastatic nodules in the routine one-plane approach; however, most cases are not quite that simple and might require lateral and oblique tomography, particularly for evaluation of hilar involvement. The brevity of this statement does not indicate that chest tomography is unimportant. On the contrary, the individual approach can yield essential information for the physician. If the use of tomography is over-simplified to a simple one-plane technique, less might be contributed to clinical management. A recent study suggests that lung tomography is indicated in all patients with a new diagnosis of a major primary cancer if the chest roentgenogram is normal.[1]

Imaging

In the realm of special imaging, two modalities are now in use and are actually complimentary and not competitive; ultrasonography and computerized tomography (CT). The role of these imaging techniques will be discussed together even though they are different in physical principles.

The computerized tomograph was a natural instrument for simplifying the approach to evaluation of head and neck cancer diagnosis as a non-invasive technique. It is the simplest approach in evaluating both primary and secondary new growth within the cranial fossa using both unenhanced and enhanced (intravenous iodides) techniques. It is used not only for central nervous system lesions, but is one of the best modalities for evaluating orbits. It is effective in evaluating osseous changes, not only in the cranial vault per se, but in the remainder of the head and neck. With the technical improvements in head and neck computerized tomography, the use of ultrasound for intracranial localizations and diagnosis has decreased, even though some authors (McKinney and Kosoff) still find considerable application for ultrasonography in central nervous system and cranial vault problems. In ophthalmology, globe tumors are still evaluated by ultrasonography.

In the chest and mediastinum, ultrasonography is a simple approach to evaluating chest wall lesions which can be done rapidly and less expensively than the CT scans. Ultrasonography is used to evaluate pleural effusions as well as pleural based masses. Chest evaluation of pulmonary nodules, pleural lesions, hilar masses, and in particular mediastinal lesions, computerized tomography offers the best non-invasive approach to evaluating primary and secondary new growth within these compartments. Pulmonary nodules are found with relative ease when compared with the individualized approach to chest tomography. Minimal pleural changes are depicted readily. And as intimated, the mediastinum, for the first time, is relatively satisfactorily investigated by means of a non-invasive technique. Not only is the CT used in the initial workup, but provides a method of following the results of therapy. For lesions of the chest and mediastinum as well as within the abdomen, computerized tomography is probably the simplest approach to radiation therapy field-planning.

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In the abdomen, both ultrasonography and computerized tomography are important. In large and obese patients, computerized tomography is the modality of choice, for fat acts as a relative contrast medium by virtue of its radiotranslucency. In contrast, in ultrasonography, the fibrous interfaces within fat often act as a hindrance. The reverse is true in thin patients where the demarcation planes are seen to better advantage in ultrasonography and are frequently lost in computerized tomography. In the normal sized patient, either approach may be used for evaluating the retroperitoneum and intraperitoneum. Computerized tomography has the advantage that gas is less of a problem than with ultrasound.

In organs such as the liver, computerized tomography can cover the entire structure with ease, but internal resolution is not as anatomically complete as in ultrasonography. The same is true for the spleen, even though the latter is more easily examined by computerized tomography in view of gas in the colon and stomach. The simplest approach to evaluating adrenal beds is by CT scanning, but in using the Sample technique, the adrenal is well delineated in ultrasound as well.

The most obvious use for either imaging modality is in evaluating the possibility of adenopathy in various primary cancers in the retroperitoneum and intraperitoneum. Both approaches compare favorably when performed by experienced examiners. In ultrasound, the ability of the examiner varies on a person-to-person basis in contrast to CT scanning.

Ultrasound does have an advantage in differentiating between intraperitoneal masses in contrast to CT. Ultrasonography is used for initial pancreatic and renal scanning. CT scan is frequently required in the pancreatic bed because of gas problems. Renal examinations might frequently require CT scanning because of technical ultrasound limitations. Pelvic scanning in the reproductive age is obviously an ultrasound approach; however, because of intestinal gas problems and the necessity for a full bladder in ultrasound, CT scanning has many advantages.

The skeletal system is initially approached by routine radiography and/or nuclear scans. In evaluating the actual extent of bone involvement by tumor, CT scanning with special techniques has a large role to play, particularly in the future. Extremity studies with both ultrasound and CT scanning are important. In soft tissue lesions, resolution is excellent by both modalities. In the bony component, however, CT scanning is preferred.

The approaches to cancer diagnosis and followup by ionizing and nonionizing imaging procedures have altered dramatically the management of patients with cancer. By careful individualizations of the needs of each patient, earlier diagnoses can aid in the cure of cancer, and definition of the extent of the tumor aids in the selection of the most appropriate methods of treatment.

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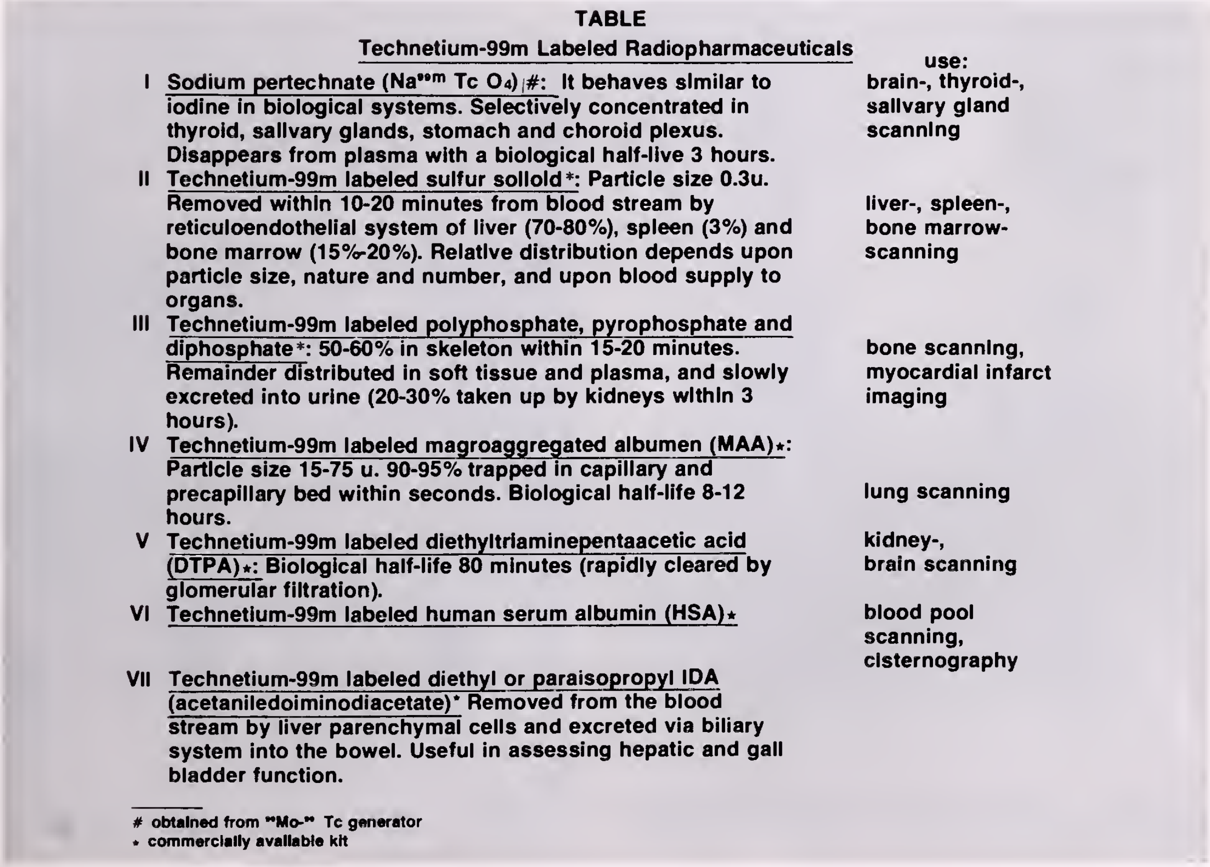
Role of Nuclear Medicine in Oncology

MERLE K. LOKEN, M.D., Ph.D.* and MATHIS P. FRICK, M.D.*

THE MAJOR ROLE of radionuclides in clinical oncology relates to tumor detection[1]. This may be achieved with various radiopharmaceuticals chosen because of their specificity for localizing in various body organs, or as "tumor seeking" agents. In addition to tumor detection, radionuclides are employed in oncology to aid in the staging of malignant disease, and to make subsequent assessments of response to treatment[2].

In addition to being organ or tumor specific, radioactive materials must emit gamma ray photons suitable for detection by sodium iodide crystals used in rectilinear scanners and scintillation cameras, which produce scintigrams of the distribution of radioactivity in the body. The scintillation camera is preferred for these studies because it views the selected area of the body continuously and thus may be used to assess changes in the distribution of radioactivity with time, thereby providing functional information, if desired. With the aid of computer analysis, currently an integral part of many procedures, quantitative information on regional function and blood flow can also be obtained for most body organs.

Radionuclides are usually administered intravenously in tracer quantities and, therefore, produce no pharmacological effects. Since the information content in scintigrams is governed by the number of gamma events which produce the picture, one must use millicurie quantities of radioactivity per patient study. To keep the radiation exposure to a minimum, the nuclide used should have a relatively short half-life. Physical half-lives of several hours to several days result in acceptable radiation doses, permit transporta-



TABLE

	Technetium-99m Labeled Radiopharmaceuticals	use:
I	Sodium pertechnate (Na^{99m} Tc O$_4$)#: It behaves similar to iodine in biological systems. Selectively concentrated in thyroid, salivary glands, stomach and choroid plexus. Disappears from plasma with a biological half-live 3 hours.	brain-, thyroid-, salivary gland scanning
II	Technetium-99m labeled sulfur colloid*: Particle size 0.3u. Removed within 10-20 minutes from blood stream by reticuloendothelial system of liver (70-80%), spleen (3%) and bone marrow (15%-20%). Relative distribution depends upon particle size, nature and number, and upon blood supply to organs.	liver-, spleen-, bone marrow-scanning
III	Technetium-99m labeled polyphosphate, pyrophosphate and diphosphate*: 50-60% in skeleton within 15-20 minutes. Remainder distributed in soft tissue and plasma, and slowly excreted into urine (20-30% taken up by kidneys within 3 hours).	bone scanning, myocardial infarct imaging
IV	Technetium-99m labeled magroaggregated albumen (MAA)*: Particle size 15-75 u. 90-95% trapped in capillary and precapillary bed within seconds. Biological half-life 8-12 hours.	lung scanning
V	Technetium-99m labeled diethyltriaminepentaacetic acid (DTPA)*: Biological half-life 80 minutes (rapidly cleared by glomerular filtration).	kidney-, brain scanning
VI	Technetium-99m labeled human serum albumin (HSA)*	blood pool scanning, cisternography
VII	Technetium-99m labeled diethyl or paraisopropyl IDA (acetaniledoiminodiacetate)* Removed from the blood stream by liver parenchymal cells and excreted via biliary system into the bowel. Useful in assessing hepatic and gall bladder function.	

# obtained from ^{99}Mo-^{99} Tc generator

* commercially available kit

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*Division of Nuclear Medicine, Department of Radiology, University of Minnesota Medical School, Minneapolis.

tion from the site of production and provide a reasonable self-life for biological phenomena under study.

Most radionuclides are attached to specific organic molecules to become more tissue specific. The principal radionuclide used today is 99-m Technetium, either in its organic form or combined with one of several organic molecules (Table).

Although a radionuclide image may show areas of abnormally increased or decreased activity, such a revelation is not necessarily specific for the presence of malignant disease. Primary or metastatic tumors, osteomyelitis, fractures or Paget's disease may result in "hot spots" on bone scans requiring clinical or radiographic correlation (Figure 1)[3]. Tumors embedded in organs which take up specific radiopharmaceuticals (e.g., during liver scanning with radiocolloid) become a cold volume surrounded by radioactivity in the normal parenchyma. These lesions may be difficult to detect and depend upon size and location to differentiate from other space occupying lesions, such as abscesses and hematomas. Passive diffusion of 99-m Technetium Pertechnate (and DTPA) from high concentration in the blood to low concentration in areas of compromised "blood brain barrier" results in abnormally increased radioactivity. This occurs with primary and secondary brain tumors, as well as with cerebrovascular accidents, abscesses or encephalitis.

Desirable biological characteristics of a radiopharmaceutical for tumor imaging include high tumor specificity and rapid clearance from surrounding tissues and circulating blood. A high tumor to non-tumor ratio facilitates the identification of small tumors and minimizes the number of false negative studies. In practice, there are few tumor seeking radionuclides. The nuclide which comes the closest to satisfying this criterion is 67-Gallium[5]. Radio-labeled antitumor agents as Bleomycin also show promise in this regard[4].

67-Gallium appears to be of value in staging and followup evaluation of lymphomas, malignant melanomas and tumors of the lung, breast, liver, brain and testicle (Figure 2). Knowledge of normal 67-Gallium distribution and excretion and of the nature of "false positive" results (e.g., abnormal uptake of 67-Gallium in a variety of benign conditions) is

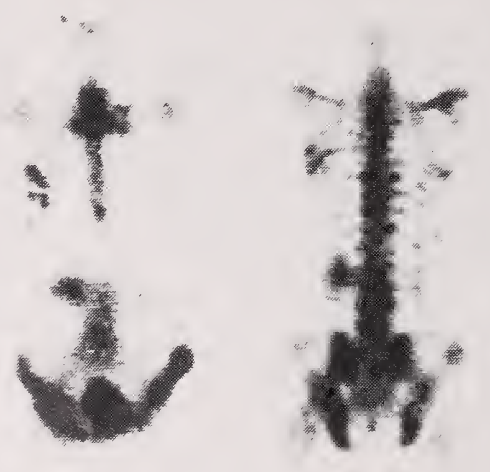

Fig. 1(A) — Anterior (left) and posterior (right) bone scan in a 75 year old male with prostatic carcinoma. Classic metastatic pattern and characteristics of right ureteral obstruction.

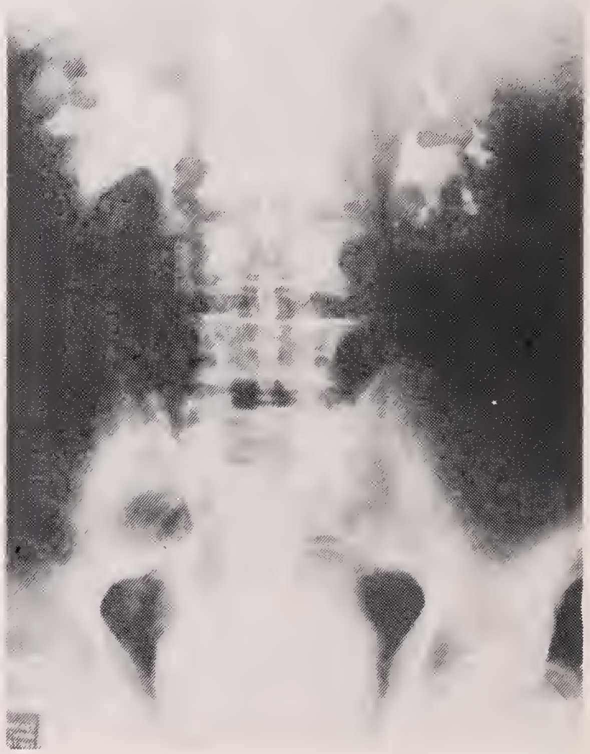

Fig. 1(B) — Presence of ureteral obstruction confirmed by intravenous pyelography.

essential for correct interpretation. Information acquired by 67-Gallium imaging remains, therefore, complementary to that derived from other oncologic diagnostic modalities.

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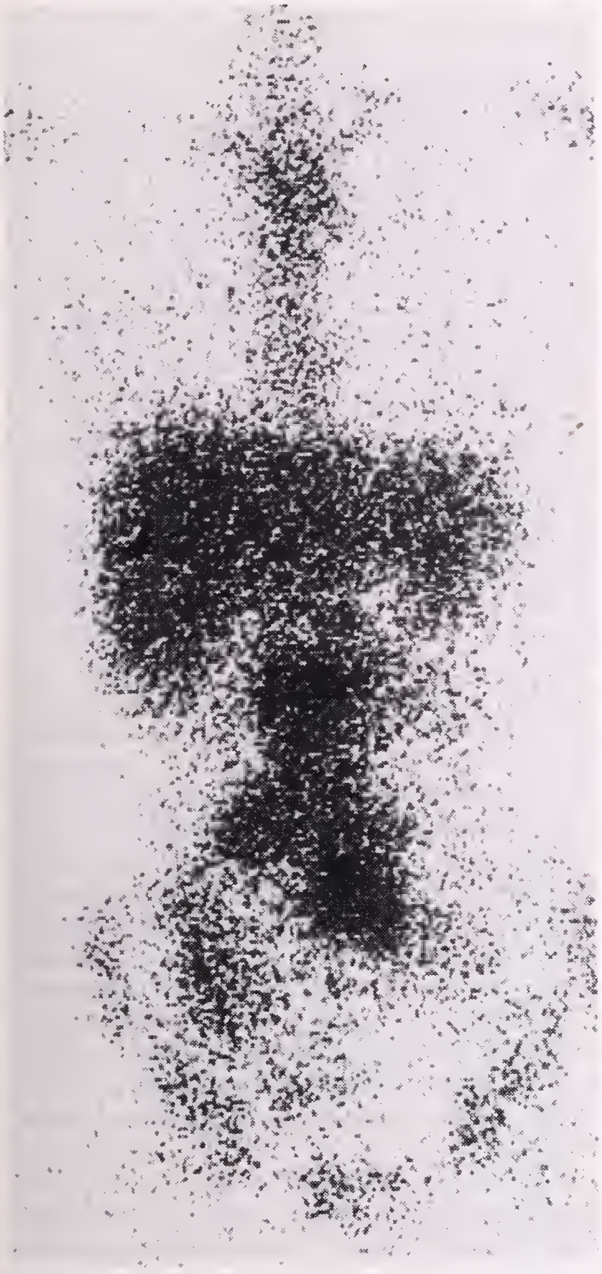

Fig. 2(A) — 67-Ga body scan in a 22 year old female with Hodgkin's disease, lymphocyte predominant type, stage IIB. Normal 67-Ga uptake in axial skeleton, liver and spleen and abnormal 67-Ga accumulation in iliac and paraaortic lymphnodes.

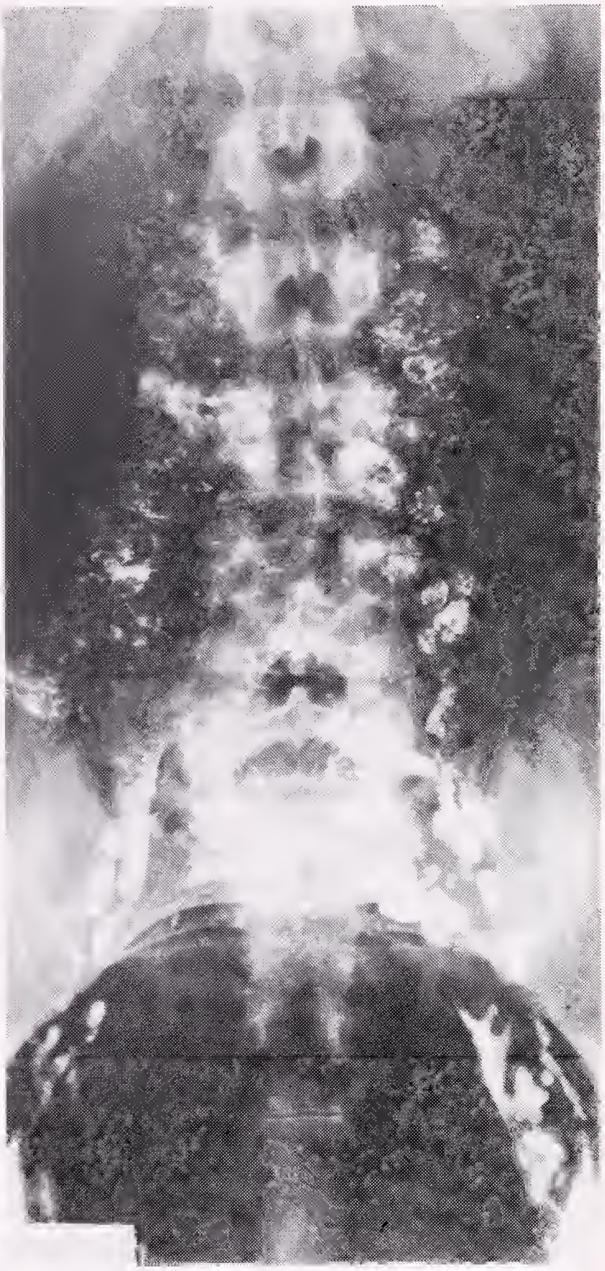

Fig. 2(B) — Lymphangiogram confirms huge "foamy" iliac and paraaortic lymphnodes.

Role of Gastrointestinal Endoscopy and Peritoneoscopy in the Diagnosis of Cancer

I. DODD WILSON, M.D.*

THE DIAGNOSIS of esophageal, gastrointestinal, pancreatic and hepatobiliary malignancies has been facilitated greatly by improvements in endoscopic equipment and techniques. In contrast to fifteen years ago, a preoperative histologic diagnosis of most esophageal, gastric, ampullary and colonic malignancies is now made. The pathologic anatomy of biliary tract and pancreatic carcinoma also can be defined before surgery. Detection of early gastric and colonic cancers, using endoscopy, seems to be practical in populations having a high risk. Finally, although results of well-designed studies which compare x-ray and endoscopy are not available, the concensus of gastroenterologists seems to be that endoscopy is more accurate in the diagnosis of upper and lower gastrointestinal lesions.

Improvement in endoscopic results has been due primarily to advances in endoscopic skills and instrumentation coupled with innovative new approaches to difficult problems. Endoscopes have become highly flexible, easily directed, smaller in diameter and adaptable to a variety of purposes. Biopsy, cytology, photography, cholangiopancreatography and therapeutic procedures, such as polypectomy and endoscopic retrograde sphincterotomy, now can be accomplished with endoscopy. Patient acceptance of endoscopic procedures has improved as techniques have become less uncomfortable. Finally, it is my impression that the morbidity of endoscopic procedures has declined.

Upper Gastrointestinal Endoscopy

When endoscopic biopsy and cytology are both used, histologic diagnosis of squamous cell carcinoma of the esophagus can be made preoperatively in almost all cases. Biopsy alone, when negative, may be misleading because of the tendency of these tumors to infiltrate deep to the mucosa and, therefore, the site of biopsy. Cytology often will yield positive results when this situation occurs. Unfortunately, accuracy in diagnosis does not appear to have improved the poor prognosis of esophageal cancer, presumably because these tumors often are in an advanced stage when they become symptomatic. Because of this poor prognosis, palliation aimed at maintaining the patency of the esophagus becomes important. Esophagoscopy is employed in assessment of the degree of patency and sometimes in placing a guide wire through the narrowed lumen to faciliate dilation of the diseased esophagus.

As with carcinoma of the esophagus, the histologic diagnosis of advanced adenocarcinoma of the stomach is made in most cases using biopsy, sometimes in conjunction with cytology. At least six biopsies should be taken from each suspicious lesion. Gastroscopy has proven to be especially valuable in defining the nature of equivocal or unusual findings on x-ray which are suggestive of cancer, often helping to avoid an unnecessary surgical procedure. In addition, the finding of a malignant gastric lesion at endoscopy in a patient with a previously normal upper gastrointestinal series is not an uncommon experience. Gastroscopy can differentiate lymphoma, with its better prognosis and different therapy, from adenocarcinoma.

In Japan, where adenocarcinoma of the stomach is the leading cause of death from cancer, earlier detection has proven feasible. In some Japanese institutions, about 1/3 of gastric cancers are detected when still localized to the mucosa and submucosa. These patients have a good prognosis. Unfortunately, the diagnosis of early gastric cancer is uncommon in this country, even when patients are known to have diseases, such as pernicious anemia, which have a high risk.

The role that endoscopy should play in the management of gastric ulcers which appear benign at x-ray is unclear. About 3% of radiologically benign-appearing gastric ulcers will eventually prove to be malignant. Some gastroenterologists endoscope all patients with gastric ulcer, whereas others take a more conservative approach, reserving gastroscopy for those patients whose ulcer does not heal at a satisfactory rate.

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Endoscopic Retrograde Cholangiopancreatography (ERCP)

Radiologic evaluation of the pancreatic and biliary ducts, using ERCP, has proven to be a major advance in the evaluation of the patient with symptoms, physical signs and/or laboratory findings suggestive of pancreatic or biliary-tract cancer. Silvis et al.[1] were able to cannulate the appropriate duct in over 85% of patients having these malignancies. After cannulation was accomplished, the diagnostic accuracy was over 90%. DiMagno et al.[2] found a similar high specificity rate for ERCP in the diagnosis of pancreatic cancer. The ability to differentiate malignant from benign disease and to define the pathologic anatomy of these cancers has made treatment of these patients more logical. Operation is avoided for some, while for others, precise preoperative information allows for more effective surgery. As with esophageal carcinoma, however, better diagnosis does not appear to have improved the generally dismal prognosis of these tumors. ERCP has morbidity of between 1 and 2%, mostly mild acute edematous pancreatitis. Transhepatic cholangiography may prove to be preferable to ERCP in studying some patients with biliary tract disease but the necessary comparative studies remain to be done.

Colonoscopy

Carcinoma of the colon is the most common visceral malignancy in the United States, causing almost 50,000 deaths annually.[3] Slightly more than half of these tumors are within reach of the standard 25 cm. proctosigmoidoscope. Although routine proctosigmoidoscopy has been recommended as a screening procedure for rectal and rectosigmoid carcinoma in patients over age 40, this recommendation is often ignored. An obvious reason is that when asymptomatic patients with a negative rectal exam are studied, only one in a thousand is likely to have a cancer diagnosed. Many physicians probably are unwilling to do 1000 proctosigmoidoscopies to find one cancer. The opposite side of the argument is that cancers found by proctosigmoidoscopy in asymptomatic patients generally have an excellent prognosis. In addition, a higher percent of asymptomatic people will have either benign adenomatous polyps or villous adenomas found. Removal of these polyps may reduce the incidence of subsequent cancer.[4]

An effective method of screening for colonic cancer is needed. Recently, Bond and Gilbertsen[3] have presented preliminary data from a study at the University of Minnesota using impregnated guaiac slides to test for occult blood in stools according to Greegor's protocol. This study is an ongoing, randomized evaluation of 45,000 subjects, ages 50-80. Of the first group studied, 1.8% had at least one stool positive for occult blood and 13.7% of these were found to have colon or rectal cancer. Sixty-nine percent of the cancers were Duke's A stage which has a favorable prognosis. Colonic polyps were found in 30% of those with occult bleeding. Of tumors beyond the reach of proctosigmoidoscopy, 41% of carcinomas and 55% of benign polyps were not diagnosed on routine barium enema. Although air contrast barium enema probably would have yielded better results, these data indicate that colonoscopy is essential to the evaluation of these patients. Although the preliminary results appear promising, assessment of the impact of such screening on survival of these patients must await longer follow-up.

Peritoneoscopy

Interest in peritoneoscopy in order to study non-gynecologic intraperitoneal disease appears to be increasing. Using peritoneoscopy, the liver surface, gallbladder, spleen, peritoneum, pelvic organs and diaphragm can be visualized. Photography, biopsy, brush cytology, and even injection of contrast agents into the biliary, vascular and lymphatic systems for radiographic study are possible. Contraindications to peritoneoscopy include ileus, uncorrectable bleeding disorders, recent acute myocardial infarction, and an uncooperative patient. Previous abdominal surgery increases the risk of the procedure and decreases visualization due to the presence of adhesions, but usually does not prevent an adequate endoscopic exam. Peritoneoscopy has an associated complication rate of 2.5%, usually mild in degree, and an associated mortality rate of 0.03%.

Relative to cancer, the value of peritoneoscopy includes diagnosis, staging, and defining the possibility of curative surgery in some patients. Peritoneoscopy is especially valuable in the diagnosis of hepatic malignancy where the 40% positive yield from a single percutaneous liver biopsy can almost be doubled. Lesions localized to the left lobe are especially well studied with peritoneoscopy. One goal of peritoneoscopy, which can often be accomplished, is to make a difficult diagnosis or to stage malignant disease without resorting to exploratory surgery.

Discussion and Summary

Endoscopy has provided a method for obtaining an accurate preoperative diagnosis of most cancers arising from the gastrointestinal tract, liver, pancreas and biliary system. Since good patient management requires correct diagnosis, the care given to these patients should be improved. Establishing the diagnosis facilitates the proper selection of patients for surgery and allows termination of prolonged, uncomfortable and expensive evaluations. Although endoscopic procedures are expensive, some cost savings arise from more expeditious care and from the avoidance of unnecessary surgical procedures. Examples of the latter include exploratory laparotomies previously performed: (1) to exclude malignancy, (2) to remove benign colonic polyps (3) to stage some lymphomas that can be staged with peritoneoscopy, and (4) to diagnose malignancies when liver metastases are already present.

Unfortunately, an improvement in survival has not been demonstrated to have resulted from the accurate diagnosis of these tumors in this country. Endoscopy, unless routinely applied to the general population, probably could not be expected to achieve early diagnosis since it is used almost solely to study patients who already have symptoms caused by their cancer. The real promise for early diagnosis lies in the use of endoscopy to study populations identified by other screening procedures as having a high incidence of a particular tumor. Examples of this approach include screening for precancerous changes in patients with ulcerative colitis and, in the study described above, using detection of occult colonic bleeding to screen for colonic cancer.

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Continuing Medical Education

Hand Symposium

The Third Annual John R. Sebald Memorial Hand Symposium, sponsored by Bethesda Lutheran Medical Center, a seminar for primary care physicians, surgeons, nurses, occupational and physical therapists, will be held Friday, September 28, 1979 in the O'Shaughnessey Education Center at the College of St. Thomas in St. Paul.

The featured speakers are: Richard Smith, M.D., Chief of Hand Surgery Services, Massachusetts General Hospital, Boston, Massachusetts. Joseph Kutz, M.D., Clinical Professor of Surgery, University of Louisville, Louisville, Kentucky and Allen Van Beek, M.D., Associate Professor of Plastic and Reconstructive Surgery, University of Southern Illinois, Springfield, Illinois.

Application has been made for Category I credits, American Medical Association, American Academy of Family Practice and Minnesota Nurses Association continuing education credit.

There will again be an afternoon workshop for physical and occupational therapists to emphasize rehabilitation and splinting methods for diseases and deformities in the hand.

For information on registration contact Tim Hanson, Associate Administrator, Bethesda Lutheran Medical Center, 559 Capitol Boulevard, St. Paul, Minnesota 55103, (612) 221-2395.

Estrogen Receptors in Breast Cancer

DAVID T. KIANG, M.D., PH.D.*

IN 1961, FOLCA, ET AL. demonstrated that breast cancers with a high uptake of radioactive estrogen responded to adrenalectomy and oophorectomy, in contrast to little response in those with low or no uptake. Since then, cytoplasmic substances called estrogen receptors responsible for the uptake and retention of estrogenic compounds were identified. A breast tumor lacking estrogen receptors will not respond to endocrine therapies because its growth is independent to the host hormonal status. On the contrary, breast tumors containing a significant amount of estrogen receptors have a 60% chance of being controlled by hormonal therapy.[1]

Methodology

Tissue Collection and Transportation

Since estrogen receptors are extremely heat labile, exposure of tissue in room temperature even for a short period (ten minutes) will significantly reduce estrogen receptor activity. Immediately after the removal of the necrotic, fatty and connective tissues, the tumor should be cut into small pieces and quickly frozen in cryostat, or preferably, in liquid nitrogen. According to our experience, the incidence of positive estrogen receptors in tissues collected and transported in liquid nitrogen is significantly higher than those collected and transported in dry ice.

Assay Method

The two most frequently used techniques in determination of estrogen receptors are the sucrose gradient method and the dextran coated charcoal method (DCC). Each method has its merits and is complimentary to each other. The sucrose gradient method can separate the 8 S and 4 S components of the receptors. Only the 8 S type of estrogen receptors has significantly correlated with clinical responses.[2] This method is currently used only for research purposes because it is expensive in terms of time consumption and equipment requirements such as ultracentrifuge. For routine estrogen receptor assay, the DCC method is economical and can provide enough pertinent information to predict the clinical response. The DCC method can further be simplified by using a single saturation dose.

Interpretation of the Results

Since the methodology varies from one institute to another, the standard used to call a positive estrogen receptor is also different. At the time of interpretation of the results, factors such as hormonal status, type of hormonal therapy, and sources of tissue should be taken into consideration.[3] Tissues known to contain estrogen receptors, such as rat uterus, should be used as positive control during the assay.

Role of Estrogen Receptors

(A) Prediction for hormonal response of breast tumor:

Approximately 50-60% of postmenopausal breast tumor and about 40% of the premenopausal breast tumor contain a significant amount of receptors. Of these receptor-rich tumors, approximately 60% of them will respond to either endocrine surgery such as oophorectomy or additive therapy; while only 5% of receptor-poor tumors will respond.[1]

(B) Potential usefulness in the differential diagnosis of adenocarcinoma of unknown primary:

The 8 S-type receptors have been found mainly in the cancer of the breast, uterus, and ovaries. Although high affinity estrogen binding was found in other types of adenocarcinoma, the nature of this binding was uncertain and some were found to be 4 S-type receptors. With the assistance of clinical information, the presence of 8 S-type receptors in adenocarcinoma would be helpful in the determination of the primary site.[4]

(C) Understanding the mechanism of action of estrogens:

Discovery of the receptors has changed the concept of steroid hormone action. It is not the steroid hormone per se, but the receptor which activates the RNA, DNA and protein synthesis. The function of steroid hormone is merely to transform the receptor into a configuration able to translocate into the nucleus and bind to the chromatin. Furthermore, study of the nuclear estrogen receptors might clarify the mechanism of anti-tumor effect from additive hormonal therapy.

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*Section of Medical Oncology, Department of Medicine, University of Minnesota School of Medicine, Minneapolis, Minnesota.

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Other Biological Markers in Breast Cancer

Since approximately 40% of estrogen receptor-rich tumors do not respond to hormonal therapy, search for other biological markers to improve the prediction rate is indicated. Progesterone receptor is considered to be one of the end-products from estrogen stimulation in the target tissues. The presence of progesterone receptors might indicate the responsiveness of the tissues to estrogen. In breast cancers containing both estrogen and progesterone receptors, approximately 80% of them respond to the hormonal therapies. However, in estrogen receptor-rich but progesterone receptor-poor tumors, 40% of them still respond to hormonal therapy. Therefore, clinical management should not depend upon the results of progesterone receptor alone. A combination of estrogen receptor and progesterone receptor assay may improve the prediction of the response.[5]

Nuclear estrogen receptors are another biological marker which are currently under investigation. Since nucleus is the primary site of receptor action, determination of nuclear receptors may be more promising than cytosol receptor assay in the prediction of hormonal response. However, the methodology of nuclear receptor assay is still subject to further improvement.[6]

General Information

1. Estrogen receptors do not correlate with the clinical stage of breast cancer.

2. Correlation of estrogen receptor with histological types of breast cancer is still under investigation. Lobular carcinoma was found to have a high incidence of containing a significant amount of estrogen receptors.

3. Incidence of estrogen receptor-rich in primary breast lesion is slightly higher than that in the metastatic lesions. Receptor assay should be performed at the time of mastectomy so the result can be banked for future use. The metastatic lesions may not be accessible in many instances at the time of recurrence. However, all the accessible metastatic lesions should also be biopsied for estrogen receptor study because they are more informative than the primary lesions.

4. Evolution of estrogen receptor from positive to negative does occur, especially after effective hormonal therapy.

5. Tumor estrogen receptor status might also be useful in predicting the response to cytotoxic chemotherapy.[7]

Our study revealed that 86% of receptor-rich tumors responded favorably to cytotoxic chemotherapy, while only 36% of receptor-poor tumors responded ($p<0.001$). Those tumors found to be persistently receptor-rich at the later phase of the disease or following previous hormonal therapy have even a better probability (up to 93%) in responding to chemotherapy. Contrary results[8] have also been reported which might be derived from a biased patient selection.

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Continuing Medical Education

The scheduled meetings of the Minnesota Urological Society, Inc. for 1979-1980 are as follows:

Pyelogram Conferences:	November 16, 1979 January 18, 1980 February 15, 1980 March 14, 1980	L'hotel de France Minneapolis, MN
Fall Seminar:	September 13-16, 1979 Brainerd, MN	
Spring Seminar and Annual Meeting:	April 19, 1980 L'hotel de France Minneapolis, MN	

B & T Markers in Leukemia and Lymphoma

CLARA D. BLOOMFIELD, M.D.*

IN RECENT YEARS our understanding of the immune system has greatly increased. Through the study of surface membrane markers, morphologically indistinguishable small lymphocytes have been found to be of two general types, thymus dependent lymphocytes or “T” cells and thymus independent lymphocytes or “B” cells[1]. These two types of lymphocytes appear to mediate different kinds of immune responses and localize in different anatomic sites. B cells primarily mediate humoral immunity; in the lymph node they are distributed in the far cortex, the follicles and the medullary cords. T cells primarily mediate cell-mediated immunity and anatomically are found in the paracortex.

The complexity of the immune system is increasingly being recognized. Most immunologic functions appear to be the result of complicated interactions of both the B and T systems. B and T cell populations in reality contain a number of subpopulations. Even methods of identification of cells as B or T appear to be more difficult than previously thought. However, the application of lymphocyte surface marker (LSM) analysis to the study of human lymphoid malignancies seems to have clinical relevance including diagnostic, prognostic and therapeutic utility.

Numerous techniques are available for studying membrane surface markers. The ones most commonly used in characterizing malignant cells as B or T are sheep erythrocyte receptors (E), surface immunoglobulin (SIg), complement receptors (C′) and FC receptors. E are usually evaluated by rosette formation with unsensitized sheep erythrocytes. SIg is identified by immunofluorescence using monospecific antisera against heavy $(\gamma\ \mu, \alpha, \delta)$ and light (κ, λ) chains. C′ are identified by the EAC′ rosette assay and Fc receptors are studied using immunofluorescence with aggregated human IgG. Normal B lymphocytes are characterized by the presence of SIg; there is a subset of B cells which contain C′ and Fc receptors. T lymphocytes are characterized by the presence of E.

In the immunologic classification of leukemia or lymphoma,[2] B cell disorders are those where the malignant cells demonstrate C′ and monoclonal SIg or only monoclonal SIg. Monoclonal indicates that the malignant cells carry on their surface only one heavy and one light chain. T cell disorders are those where the malignant cells form rosettes with unsensitized sheep erythrocytes. “Null cell” disorders are those where the malignant cells do not demonstrate monoclonal SIg, E or C′.

Immunologic classifications of lymphoproliferative disorders have been most widely applied in acute lymphocytic leukemia (ALL). In recent years therapeutic advances in ALL have resulted in 50% of children being cured and 50% of adults surviving disease free for greater than 3 years. This striking improvement in treatment outcome has shifted the therapeutic goals in ALL to the identification of good responders, for whom relatively minimal treatment achieves cure, and poor responders, for whom current therapeutic approaches are inadequate and new ones must be developed.

Among the prognostic tools that appear to be useful in separating good and poor responders are clinical characteristics, morphology and various biologic markers, including LSMs, cytogenetics, enzymes and hormone receptors. At the current time, LSMs appear to be the most useful of these prognostic tools.

The immunologic classification of ALL is shown in Table 1. When LSM marker analysis is performed on large numbers of cases of both adults and children with ALL, 75% are found to be null, 20% T and 5% B. Each of these subclasses appears to have unique clinical, therapeutic and prognostic characteristics.

TABLE 1

Acute Lymphocytic Leukemia Immunologic Classification

	E	EAC′	SIg	Fc
“Null” Cell	−	−	−	−
T Cell	+	+/−	−	−
B Cell	−	−	+	+

B cell ALL is the only subclass that is readily identifiable cytologically. The most common type of B cell ALL is “Burkitt's cell leukemia” or, using the World Health Organization (WHO) classification, immunoblastic leukemia or, using the French-American-British classification (FAB), L-3. At diagnosis the leukocyte count is usually low and there are often few circulating blasts. Tumor masses, particularly abdominal masses, are frequently present. Central nervous system involvement is frequently found at presentation or shortly thereafter. Response to treatment is generally poor; although tumor masses often rapidly melt away, disease invariably rapidly recurs. Almost all patients are dead by 6 months.

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*Associate Professor of Medicine, Section of Medical Oncology, University of Minnesota School of Medicine, Minneapolis.

T cell ALL cannot be recognized cytologically. T cell cases have been found among all of the WHO histologic subtypes except immunoblastic leukemia. Similarly, using the FAB classification, T cell cases have been found among both the L-1 and L-2 subtypes. Cytochemically, T cell ALL demonstrates characteristic acid phosphatase positivity in 70% of cases, acid alpha naphthyl esterase positivity in 80%, beta glucuronidase positivity in 67%, and periodic acid-Schiff (PAS) positivity in 80%. Terminal deoxynucleotidyl transferase (TdT) levels are almost always elevated.

At diagnosis, 60% of patients with T cell ALL present with leukocyte counts >100,000/mm^3; less than 10% have counts of <20,000/mm^3. At least half of the cells in blood are usually blasts. There is a striking male predominance. The disease tends to occur in older children and younger adults. About 60% of patients present with mediastinal masses. In most patients, complete remission (CR) can be achieved. However, metabolic complications such as hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia and disseminated intravascular coagulation are common with the initiation of treatment due to rapid lysis of the enormous tumor load. Consequently, leukapheresis may be useful during initial induction to reduce the tumor load, and low doses of chemotherapy should be instituted initially. To date, remissions have tended to be short and survival is rare beyond two years.

Null cell ALL cannot be separated cytologically from T cell ALL. Cytochemically, acid phosphatase and acid alpha naphthyl esterase positivity are found in less than 10% of cases. Beta glucuronidase and PAS positivity are present in almost the same frequency as found in T cell ALL. TdT is elevated in most cases. Unlike T cell ALL, Hexosaminidase I is said to be specific for null cell ALL, but this needs confirmation.

At diagnosis 60% of patients present with leukocyte counts <20,000/mm^3; less than 10% present with counts >100,000/mm^3. Among children, a younger age predominates. There is no sex predominance. Less than 5% of patients present with a mediastinal mass. Among adults approximately 20% of patients with null cell ALL will demonstrate a Philadelphia chromosome. In both children and adults who do not demonstrate the Philadelphia chromosome almost 100% CRs result from treatment with non-intensive regimens such as vincristine + prednisone + L-asparaginase. The duration of CR tends to be long and it is possible that the majority of patients are cured.

While it appears that for ALL this immunologic classification has diagnostic, therapeutic and prognostic utility, the situation is less clear in the malignant lymphomas (MLs). LSMs definitely have diagnostic utility in ML. In undifferentiated tumors the diagnosis of lymphoma may be established by the finding of LSMs. In well differentiated lymphoproliferations the preponderance of a monoclonal B cell population differentiates lymphoma from a reactive non-malignant process where the proliferation is usually polyclonal. Similarly, when there is a lymphoid infiltration of non-Burkitt's type in the bone marrow or blood the presence of a B cell proliferation allows the differentiation of ALL from peripheralizing lymphoma.

The prognostic and therapeutic utility of LSMs are still being defined in ML. Large numbers of cases of ML have been studied for LSMs. In ML surface marker studies should be done both on suspensions of neoplastic cells and cryostat sections. Cryostat sections allow correlation of the malignant areas of the lymph node with surface markers. LSM studies have demonstrated that more than 95% of nodular lymphomas are B cell malignancies. Consequently within the nodular lymphomas, LSMs have relatively little prognostic or therapeutic utility.

Among diffuse lymphomas, however, LSMs appear to have prognostic and therapeutic utility[3]. The result of LSM studies in diffuse lymphomas are shown in Table 2. Among diffuse lymphomas about 60% are B, 10% T and 30% null. When we evaluated the ability of the histologic classes to predict survival, we found that

TABLE 2

Surface Marker Studies and the Rappaport Classification

Rappaport Classification		Surface Marker Group		
	No. of Cases	Percent of Cases		
		B	T	"Null"
Diffuse Lymphoma	53	62	8	30
IDL*	9	89	0	11
PDL	3	67	0	33
Mixed	12	67	8	25
Histiocytic	15	80	0	20
Lymphoblastic	9	0	33	67

*IDL = intermediately differentiated lymphocytic
PDL = poorly differentiated lymphocytic

patients with IDL survived significantly longer than patients with histiocytic lymphoma or malignant lymphoma lymphoblastic (MLLB). However, differences in survival among patients with other histologic subtypes were not found. In contrast, when the diffuse lymphomas were divided by immunologic classification into B and null there was a striking difference in survival ($p<0.007$). Patients with B lymphoma survived significantly longer than those with null lymphoma (Figure). Similarly, among patients with MLLB, where cases are either T or null, those patients with T lymphomas survived longer than those with null. Thus, it appears that among cases classified as diffuse, using the Rappaport system, LSM studies contribute important prognostic information not available from histology alone. Further, survival is best predicted for adults with diffuse lymphoma by combining histologic and surface marker results. In each histologic class, patients with LSM positive (B or T) lymphomas survive better than those with null lymphomas.

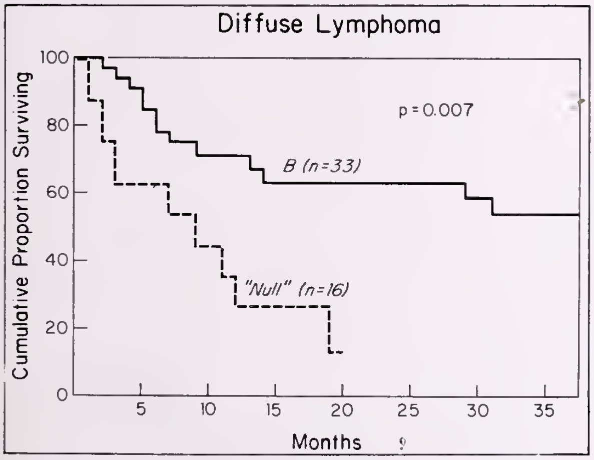

Figure — Survival of adults with diffuse lymphoma according to surface marker classification as B or Null.

Response to treatment with cyclophosphamide + vincristine + prednisone ± adriamycin among patients with diffuse lymphomas also appears to vary depending upon the immunologic type of lymphoma. In our study 69% of patients with B lymphomas achieved partial or complete remission compared to only 34% of patients with null lymphomas ($p<0.025$.) Thus, at least with the above treatment regimens B lymphomas appear to respond better than null lymphomas.

In summary, current evidence suggests that LSM studies have clinical relevance in ALL and ML. When studying blood and bone marrow LSMs have diagnostic utility for differentiating ALL from acute non-lymphocytic leukemia, peripheralizing lymphoma and reactive processes. When studying lymph nodes and other tumor masses LSMs are useful for differentiating ML from undifferentiated carcinoma and reactive non-malignant processes. LSMs also have prognostic utility. Among patients with ALL survival is best for cases classified as null, intermediate for cases classified as T and poorest for cases classified as B. Many cases of null cell ALL may be cured. Among diffuse lymphomas, survival is best for those that are B, intermediate for those that are T and poorest for those that are null. Preliminary data suggests that LSMs also have therapeutic utility. In ALL it appears that patients with null-ALL can be cured with standard therapy, while new approaches are required for those with T or B ALL. At the current time, LSM studies are critical for all cases of ALL and probably should be performed in all patients with diffuse lymphoma.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect; rather, the drug should be discontinued. Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly. *Drug Dependence*: Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion. The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks. *Use in Children*: Tenuate is not recommended for use in children under 12 years of age.

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema. *Endocrine*: Impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria.

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg. tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg. tablet daily, swallowed whole, in midmorning. Tenuate is not recommended for use in children under 12 years of age.

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Product Information as of April, 1976

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References: 1. Citations available on request — Medical Research Department, MERRELL RESEARCH CENTER, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M.T., O'Dillon, R.H., and Leyland, H.M. A Comprehensive Review of Diethylpropion Hydrochloride. International Symposium on Central Mechanisms of Anorectic Drugs, Florence, Italy, Jan. 20-21, 1977.

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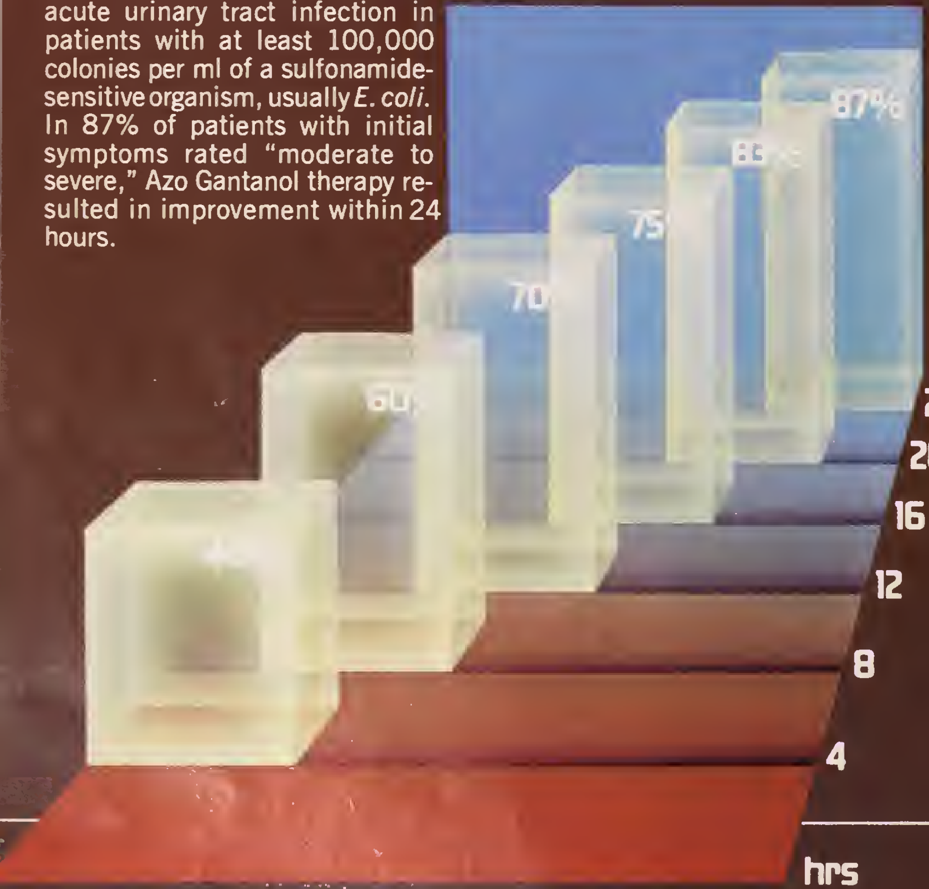

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Contraindications: Children below age 12; su fonamide hypersensitivity; pregnancy at term during nursing period; because Azo Gantanol tains phenazopyridine hydrochloride it is cont dicated in glomerulonephritis, severe hepatiti uremia, and pyelonephritis of pregnancy with disturbances.

Warnings: Safety during pregnancy not establ Deaths from hypersensitivity reactions, agran tosis, aplastic anemia and other blood dyscra have been reported and early clinical signs (s throat, fever, pallor, purpura or jaundice) may dicate serious blood disorders. Frequent CBC urinalysis with microscopic examination are ommended during sulfonamide therapy.

Precautions: Use cautiously in patients with paired renal or hepatic function, severe aller bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria stone formation.

Adverse Reactions: *Blood dyscrasias* (agran-ulocytosis, aplastic anemia, thrombocytope leukopenia, hemolytic anemia, purpura, hyp thrombinemia and methemoglobinemia); *all reactions* (erythema multiforme, skin eruptic Stevens-Johnson syndrome, epidermal necr urticaria, serum sickness, pruritus, exfoliati dermatitis, anaphylactoid reactions, periorb edema, conjunctival and scleral injection, p sensitization, arthralgia and allergic myoca *G.I. reactions* (nausea, emesis, abdominal hepatitis, diarrhea, anorexia, pancreatitis a stomatitis); *CNS reactions* (headache, peri neuritis, mental depression, convulsions, a hallucinations, tinnitus, vertigo and insomn *miscellaneous reactions* (drug fever, chills, nephrosis with oliguria and anuria, peria nodosa and L. E. phenomenon). Due to ce chemical similarities with some goitrogens, uretics (acetazolamide, thiazides) and oral glycemic agents, sulfonamides have caus instances of goiter production, diuresis and glycemia. Cross-sensitivity with these agen exist.

Dosage: Azo Gantanol is intended for the painful phase of urinary tract infections. *Us adult dosage:* 2 Gm (4 tabs) initially, then (2 tabs) B.I.D. for up to 3 days. If pain per causes other than infection should be soug After relief of pain has been obtained, cont treatment with Gantanol (sulfamethoxazole be considered.

NOTE: Patients should be told that the ora dye (phenazopyridine HCl) will color the u

Supplied: Tablets, red, film-coated, each ing 0.5 Gm sulfamethoxazole and 100 mg phenazopyridine HCl—bottles of 100 and 5

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Chorionic Gonadotrophin and Alpha-Fetoprotein Markers for Testicular Cancer

GEORGE J. BOSL, M.D.*

THE DISCOVERY of circulating tumor-derived substances has long been a goal of investigators seeking reliable markers of tumor activity. Perhaps the best known tumor marker is the paraprotein of multiple myeloma. Recently sensitive assays for the beta subunit of human chorionic gonadotrophin (BHCG) and alpha-fetoprotein (AFP) have become available. Either BHCG or AFP or both may be present in the serum of patients with testicular cancer and accurately reflect disease activity.

BHCG is one of two subunits of human chorionic gonadotrophin. The alpha subunit is common to several hormones, but the beta subunit is immunologically distinct, permitting the development of a highly sensitive and specific double antibody radioimmunoassay for BHCG. BHCG may be secreted by several malignancies, including approximately 60% of patients with non-seminomatous testicular cancer and is invariably elevated with the choriocarcinoma cell type.[1] It may also be found occasionally in histologically pure seminoma.

AFP is an alpha-1-globulin produced by the human fetal yolk sac and other tissues. It is present in human neonatal serum and rapidly disappears following birth. With the development of the radioimmunoassay, AFP has been detected in about 75% of patients with non-seminomatous germ cell tumors of the testis.[2] An elevated valve in a patient with testicular cancer establishes the presence of a non-seminomatous cell type.

BHCG and AFP are, therefore, common proteins associated with active testicular cancer. Approximately 90% of patients with non-seminomatous germ cell tumors of the testis will be found to have an elevated BHCG or AFP or both. Moreover, excluding metabolic decay after treatment, patients without active tumor have not had elevated levels of either marker. Thus, there are essentially no false positives and only occasional false negatives.

The measurement of BHCG and AFP may be important in clinical staging. In one study, one-third of the patients with non-seminomatous tumors and clinical Stage I disease had involved retroperitoneal nodes at lymphadenectomy or developed metastases to distant sites. 50% of these patients had elevated marker values indicating active disease.[3] Similarly elevated marker values after lymphadenectomy indicate residual disease. Thus, serial BHCG and AFP determinations may influence the staging and subsequent treatment.

For patients with Stage III disease at the time of diagnosis, the prognosis has improved dramatically during the past 20 years. Many antitumor agents have been found to be effective, and with combination chemotherapy, 60-70% of patients with Stage III disease will achieve a complete remission.[4] Most patients who are disease free at the end of two years will have a normal life expectancy. Thus, the ability to accurately assess complete remission and closely monitor the disease-free interval becomes critical. Physical examination and radiographic procedures detect macroscopic disease. Tumor marker elevations, however, may occur in the absence of measurable disease and should disappear before any remission can be complete.

Once a complete remission has been obtained, serial determinations of both markers are important. Marker values may become elevated weeks or months before the appearance of measurable disease. The reappearance of an elevated marker value implies that active disease has returned and an attempt to localize the recurrence should be undertaken so that appropriate changes in therapy may be undertaken while the tumor burden is still minimal.

Marker determinations are important in patients with seminoma as well. About 5% of patients with seminoma will have elevated serum levels of BHCG.[4] However, an elevated level of AFP is the *sine qua non* of a non-seminomatous cell type and treatment should be planned accordingly. "Pure" seminomas may be found to contain other elements on careful serial sectioning, and occasionally metastases occur which are of a different cell type. Thus, despite the high cure rate in seminomas, marker determination may alter therapy.

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BHCG and AFP are both excellent tumor markers and are present in the serum of a high percentage of men with testicular cancer. The assay is both highly specific and sensitive with only occasional false negatives and no reported false positives. The presence of these markers and any subsequent changes are reliable indicators of disease activity. All men with testicular cancer should have serial determinations of both BHCG and AFP in order to determine the extent of tumor, to follow the response to treatment and to evaluate the disease-free period.

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Adjuvant Chemotherapy of Breast Cancer

B. J. KENNEDY, M.D.*

THE EARLY DETECTION of breast cancer and the use of mastectomy for disease limited to the breast and less than 2 cm in size (Stage I) has resulted in a survival of these patients at 15 years comparable to that of a normal woman without breast cancer.[1] In Stage II breast cancer (primary tumors 2 to 5 cm in size with or without involvement of axillary nodes or less than 2 cm with axillary nodes), the relapse rate following mastectomy has been high, with only 47 to 50% of the patients being relapse free at ten years. The histologic status of the axillary lymph nodes has been the single most useful prognostic factor in breast cancer. When more than three axillary lymph nodes are involved, the ten year relapse rate is approximately 85%, with the total survival being less than 25%. These data imply that at the time of mastectomy for Stage II breast cancer, microscopic disease is already disseminated.

In an attempt to change the course of Stage II breast cancer, additional therapies have been considered. Radiotherapy has been demonstrated not to prolong survival of these patients, although it does reduce the incidence of local recurrence. The post-operative use of chemotherapy (adjuvant chemotherapy) advocated that since the chemotherapies could destroy tumor, the maximum opportunity for achieving cure of the disease would be during the early stage of the disease working with a small tumor cell burden. The studies to date suggest that adjuvant chemotherapy has a role in stage II breast cancer in pre-menopausal women.

The National Breast Cancer Task Force demonstrated that the post-operative administration of triethylene thiophosphamide resulted in a longer disease free interval in pre-menopausal women. Neissen-Meyer demonstrated that cyclophosphamide post-operatively resulted in an increased survival at ten years. The initial reports of phenyl-alanine mustard (Melphalan®) demonstrated a decreased relapse rate in pre-menopausal women.[2] This initial report stimulated a vast interest in the role of adjuvant chemotherapy.

The use of combination chemotherapy as an adjuvant chemotherapy was emphasized in the studies in Milan, Italy, by Bonadonna.[3] It is this study now at the four year level that has been followed with the greatest of interest. Other studies, however, have also confirmed the benefits that can be achieved by combination chemotherapy in the post-operative situation. Although there are defects in the various studies, the trends seem well confirmed. Adjuvant chemotherapy studies have been limited to women with Stage II breast cancer. There is no role for adjuvant chemotherapy in Stage I breast cancer. Careful definitions of the conditions for such therapy have been made in the various reports.

The Milan study has utilized cyclophosphamide, methotrexate and 5-fluorouracil in regular monthly cycles for at least one year. The recurrence rate was less in pre-menopausal women treated with CMF (25%) in contrast to an untreated control group (59%) at the four year level. The difference is statistically significant ($p=.0001$). In post-menopausal women there has been no difference in the relapse rate (44% for the treated group and 48% for the control group). The survival of all the adjuvant treated patients appears to be greater (83%) than the control group with radical mastectomy alone (74%) at the four year level, but this is not a statistically significant difference.

An explanation for the effectiveness of adjuvant chemotherapy has been postulated. In pre-menopausal women chemical castration was one consideration. This does not seem to be the sole factor. It has been postulated that in young women with reduced tumor burden, the elimination of the majority of tumor cells by the chemotherapy allows the immune system to play a role in further control of the disease. In contrast the immune system in the elderly is less effective.

It is necessary to apply to practice the results of these investigations. For women in the post-operative state with Stage II breast cancer, it is recommended that pre-menopausal women be treated with adjuvant chemotherapy. For such women it is recommended that the treatment program be thoroughly explained and emphasized that the treatment still is in the investigative phase. The long term results have yet to be completed. Because of the overall effectiveness, the treatment seems practical.

For the post-menopausal women, adjuvant chemotherapy is not recommneded, since the data shows no real benefit in this age group. Investigations are being continued in an attempt to define whether

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*Professor of Medicine and Masonic Professor of Oncology, University of Minnesota Medical School, Minneapolis, Minnesota.

A reminder

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100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
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INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout,
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age: Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

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adjuvant chemotherapy has a role in post-menopausal women, but it is strongly recommended that only those women participating in controlled research studies be managed in such a manner. Use of chemotherapy in that age group is strictly a research procedure.

The Milan investigators in interpreting their own data have stated that adjuvant chemotherapy is effective in pre-menopausal women in Stage II breast cancer. It is contended that the local recurrence rate is comparable to that obtained by post-operative radiotherapy and therefore, they do not recommend post-operative radiotherapy in the pre-menopausal patient. There is no role for immunotherapy.

Further investigations in adjuvant chemotherapy are strongly needed and are underway. It is known that patients with estrogen receptor rich tumors have a better prognosis than those with estrogen receptor poor tumors. The estrogen receptor factor was not taken into consideration in the previous adjuvant chemotherapy studies. Therefore, it is necessary that these studies be reproduced with randomization based upon the receptor content of the tumor. Such studies are underway. Further investigations are employing variations in the chemicals employed as well as the duration of treatment.

It is clear that adjuvant chemotherapy in breast cancer has introduced a major change in the concepts relative to the management of breast cancer. Individualization of patients' needs is necessary to provide a patient the optimal management of the tumor.

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Adjuvant Chemotherapy for Large Bowel Cancer

An Optimistic Appraisal

THEODOR B. GRAGE, M.D.*

SURGICAL RESECTION of colo-rectal carcinoma continues to be the primary form of therapy, though survival rates following surgical resection for this disease have plateaued during the past 20 years. Significant improvement in salvage rates in the treatment of osteogenic sarcoma, Wilms' tumor and most recently carcinoma of the breast has made the combination of surgical resection with long-term adjuvant chemotherapy increasingly attractive for a variety of solid tumors. The past history of adjuvant trials in the treatment of colo-rectal carcinoma with drug therapy is not very encouraging. The first major cooperative trial combining chemotherapy and surgery was reported by Holden in 1967 using thiotepa in the immediate postoperative period. This drug conferred no significant advantage to those patients receiving the chemotherapy.

In a prospectively controlled trial of 156 patients randomized to receive intravenous 5-FU during the intra-operative period and oral 5-FU in the postoperative period no significant treatment benefit in terms of survival or disease free interval for the group of patients receiving 5-FU was reported by Lawrence et al.

The Veterans Administration Surgical Adjuvant Group has studied over 1500 patients in a variety of programs using FUDR and 5-Fluorouracil in the form of brief postoperative courses and subsequently prolonged trials of intermittent postoperative systemic 5-FU. In the most recent trial the survival was consistently better in the treated group than in the control group, although the difference was statistically not significant.[1]

In 1971 the Central Oncology Group (COG) began to study the effect of adjuvant chemotherapy with 5-FU upon survival and recurrence rate in patients with colorectal carcinoma who either underwent a curative or a palliative resection. In those patients randomized to receive chemotherapy following curative resection significant treatment benefit was demonstrated only in those patients with an unfavorable prognosis, namely patients with Dukes C lesions and patients whose primary disease originated in the rectum.[2] This report is an update of the COG trial as of May 1978.

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Description of Study

The details of the trial have been presented elsewhere. In summary, in the curative resection group only those patients were submitted to study who had an unfavorable prognosis as indicated by penetration of the tumor through the serosa or full-thickness of the bowel wall, Dukes B, or invasion of the lymph nodes, Dukes C, or cancer in other organs removed as part of the primary resection. To the palliative group only those patients were entered in whom the primary tumor had been removed and there was histological evidence of residual tumor.

Allocation of patients to treatment group or control group was achieved by a central randomization procedure at the COG Headquarters. To insure an even distribution of unfavorable characteristics to treatment and control groups, patients were further stratified as to primary site, e.g., colon or rectum, absence or presence of lymph nodal involvement and absence or presence of obstruction at the time of operation.

Chemotherapy was started within 30 days after operation and consisted of intravenous 5-FU, 12 mg/kg/day x 4 and then 6 mg/kg on alternate days x 5, followed by 12 mg/kg/week for one year. As of May 1978, 298 patients were acceptable for evaluation, of which 217 underwent a curative resection and 82 patients underwent a palliative resection. Follow-up period ranges from 2 to 70 months, with a medium of 28 months.

Results

Severe, life-threatening toxicity, primarily related to the gastrointestinal tract was of sufficient magnitude in seven patients to discontinue therapy entirely. The remaining patients tolerated the chemotherapy well, however, some degree of leukopenia was seen in 60% of the patients, nausea and vomiting in 46% of the patients, diarrhea in 53%, and stomatitis in 20% and thrombocytopenia in 36%. There have been no drug-related deaths.

The survival curves and duration of disease free interval curves were calculated using the Kaplan-Meyer life table method and the differences in the curves between the control and chemotherapy group were evaluated statistically, using Gehans modification of the Wilcoxon test.

The survival curves and disease free interval curves for all patients in the curative group favor the chemotherapy group over the control group, however, the difference is statistically not significant. Similarly, in patients with Dukes B lesions and patients whose disease was confined to the colon, there was no significant improvement in disease free interval or survival in the chemotherapy group over the group of patients treated by surgical resection alone.

The Dukes C patients had a significantly longer disease free interval and also were favored in terms of survival when receiving chemotherapy in the post-operative period compared to those treated by surgical resection alone (Figure 1).

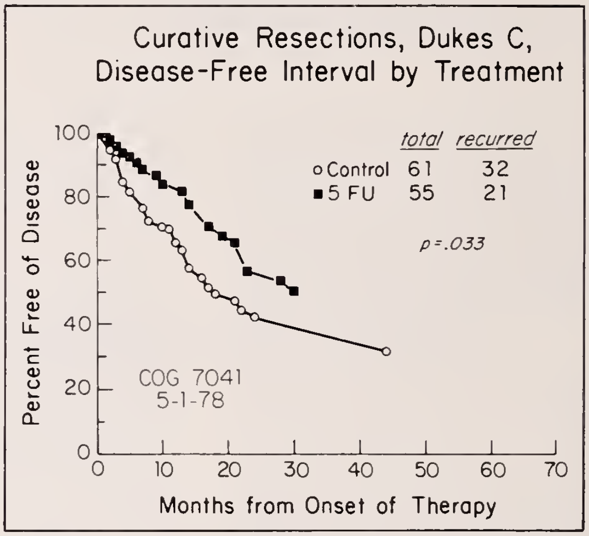

Fig. 1 — In patients with Dukes C lesions the chemotherapy group has a significantly longer disease-free interval, also survival is better, but not significantly.

Patients whose primary tumor was located in the colon had a better prognosis than patients whose primary tumor was located in the rectum. However, there was no difference between the two treatment groups in patients with primary neoplasms located in the colon.

In patients with a primary tumor located in the rectum the chemotherapy group did significantly better than the control group both in terms of disease free interval and survival (Figure 2).

It is of interest that within the chemotherapy group the leukopenic patients had a significantly longer disease-free interval than non-leukopenic patients, however, this did not translate itself into prolongation of survival although the leukopenic group was favored.

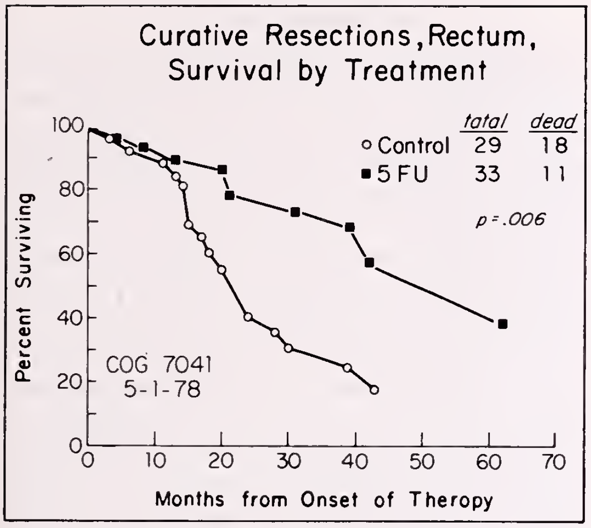

Fig. 2 — Both in terms of disease-free interval and survival, rectal cancer patients treated with 5-FU do significantly better than those treated by resection alone.

In 81 patients undergoing palliative resection there was no significant increase in survival in those who were treated with 5-FU immediately in the postoperative period versus those being treated with 5-FU after significant progression of the disease had occurred. The symptom free interval was slightly prolonged, but not significantly so.

Conclusion

We conclude that long-term administration of adjuvant chemotherapy in the postoperative period in the patient with colo-rectal carcinoma is of value only in patients with an unfavorable prognosis, namely, patients whose tumor has spread to the regional lymph nodes, or whose primary disease originated in the rectum. We also want to emphasize that the route, dose and schedule of administration is important and we recommend an initial intravenous loading course followed by weekly administration of 5-FU intravenously, for one year.

Prospects for the Future

The Eastern Cooperative Oncology Group (ECOG) is conducting a colon cancer adjuvant trial comparing 5-FU alone with a combination regime consisting of 5-FU and methyl-CCNU. Over 684 patients have been entered into this trial, but the period of follow-up is simply too brief to be meaningful. So far the recurrence rates and death rates in both groups have shown no significant differences.

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Ewing's Sarcoma

MARK E. NESBIT, JR. M.D.*

RECENT REPORTS indicate that an integrated approach to the treatment of Ewing's sarcoma of bone using local irradiation and systemic chemotherapy has significantly improved disease control and survival. Up to 15 years ago, the prognosis was dismal — less than 15% survived five years. Presently, survival in the best series is reported as 50-75% of the cases where follow-up is three to five years. The fact that the tumor is rare, as well as occurring initially in almost every bone in the body has made it difficult to accumulate a critical mass of information on the natural history and response to new therapies. For these reasons, a national study to integrate the therapy and evaluate new treatment approaches was begun in 1973 by three national study groups: Children's Cancer Study Group, Cancer and Leukemia Group B, and Southwest Oncology Group. The committee consists of: Mark Nesbit, Chairman, University of Minnesota, Minneapolis, Minnesota; E. Omer Burgert, Mayo Clinic, Rochester, Minnesota; Carlos Perez, John Kissane and Teresa Vietti, Washington University, St. Louis, Missouri; Melvin Tefft, Providence, Rhode Island; Edmund Gehan, M.D. Anderson, Houston, Texas. What factors are responsible for the improved outlook?.

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*Professor of Pediatrics and Therapeutic Radiology, University of Minnesota, Minneapolis, Minnesota.

Supported by USPHS #CA-07306.

Diagnosis and Staging

Ewing's sarcoma is one of the blue round cell tumors which is often difficult to differentiate from metastatic neuroblastoma, rhabdomyosarcoma, and lymphomas of bone. Every effort should be made to obtain viable tissues without bone at the time of biopsy. Open biopsy is the procedure of choice. Touch preparations and material for electron microscopy should be routinely obtained since the electron microscopic evaluation can help rule out neuroblastoma.

Pulmonary and bone metastases are the most common sites of spread at the time of diagnosis as well as at relapse. New computerized radiographic methods have improved our capability of assessing the extent of the primary tumor and detecting distant metastases. The incidence of lymph node and soft tissue involvement in pelvic primaries has been greatly underestimated and the use of these newer techniques as well as the introduction of surgical staging should be used more often in the initial staging of primaries occurring in the pelvis.

Adjuvant Chemotherapy

The most important change responsible for the better survival of patients with Ewing's sarcoma is the addition of systemic chemotherapy to local therapy. Initial studies showed that Vincristine, Cyclophosphamide and Actinomycin-D were effective drugs. The drugs are started at the time of local irradiation and usually continued for 18-24 months. Recently (1973-1978), the Intergroup Ewing's Sarcoma Study Committee conducted a randomized study of three treatment regimens for patients with localized Ewing's sarcoma of bone. The three treatment regimens were: Regimen 1 — Vincristine (V), Actinomycin-D (A), and Cyclophosphamide (C) plus Adriamycin (Adr); Regimen 2 — Vincristine, Actinomycin-D, and Cyclophosphamide; Regimen 3 — Vincristine, Actinomycin-D, Cyclophosphamide plus bilateral pulmonary radiation. Three hundred and fourteen patients have been entered. The results at this point in time are: (a) Overall survival for all three treatment regimens is 56% at three years, (b) The addition of Adriamycin or bilateral pulmonary radiation to Vincristine, Actinomycin-D and Cytoxan significantly improves relapse free status and survival. The major advantage is in non-pelvic patients, (c) The best treatment arm is VAC plus Adriamycin, which has a disease free status of 74% at two years, (d) Bone and lung are the major sites of relapse but there is no advantage for bilateral pulmonary radiation versus VAC plus Adriamycin in reducing lung metastases.

Local Control

Radiation therapy in combination with multiple chemotherapeutic drugs is an effective treatment method to control the primary tumor. In the Intergroup Ewing's Study, a tumor dose of 4,500-5,500 rads (age adjusted) is given to the whole bone followed by a boost dose of 1000 rads to the radiographic extent of the lesion with a 5 cm. margin. Local control of 88% has been obtained. The humerus (22%) and the pelvis (19%) have the highest incidence of local failure.

Though the dose of irradiation delivered between 4,000 and 6,500 rads does not markedly influence the rate of local control, there is a trend for a higher rate of local control with higher doses. The local control rate is the same for those patients treated with a 5 cm. free margin as those with the whole bone irradiated.[1] The following conclusions concerning the role of radiotherapy in controlling the primary lesion are: (a) The most effective dose of radiotherapy is between 5,000-6,000 rads in combination with 4 drug chemotherapy: Actinomycin-D, Vincristine, Cytoxan and Adriamycin. (b) The use of radiation therapy alone in pelvic and humeral lesions having a particularly poor local control should be questioned and possibly supplemented by the use of surgical resection. (c) Whole bone irradiation including inclusion of both epiphyseal centers might not be necessary for all primary lesions.

Prognostic Factors

Certain patient factors and characteristics seem to significantly effect the patient's chance for long term survival. Beside the occurrence of distant metastases at diagnosis which has the most unfavorable influence, the anatomic location of the primary, sex of patient and surgical history also influence survival. Using a multivariate analysis, the statistically unfavorable characteristics are a primary site in the pelvis or proximal bones, male sex and a surgical history of biopsy only. There is even suggestive data that some patients with distant metastases at diagnosis may achieve long term survival with the combination of irradiation and multi-drug chemotherapy. Recently, Vietti reported for the Intergroup Study Committee some preliminary results of treatment of 37 patients with metastatic disease who were treated with chemotherapy (Vincristine, Cyclophosphamide, Actinomycin-D, and Adriamycin) combined with irradiation to the primary lesion and up to five areas of distant radiographic involvement. Five of thirty-seven children are free of disease after eighteen months of therapy and are now off therapy.[2]

Surgical Considerations

In the past, surgery has been most often limited to initial diagnostic biopsy. However, during the last three or four years there has been a resurgence of interest in surgical procedures for treatment of the primary lesion. In the Intergroup study, a retrospective analysis of the surgical history has suggested that patients who received incomplete or complete resection had a significantly better survival. More consideration should be given in the future to the use of surgical resection for primaries in expendable bone: rib, proximal fibula and clavicle. The role of amputation is also controversial, but evidence suggests that it should be recommended for: (1) hugh destructive lesion that is otherwise unmanageable with radiation, (2) pathologic fracture and (3) a primary lesion located in the region of the distal, femoral, epiphysis or distally in a child less than six years of age. The latter is recommended because the anticipated growth retardation due to radiation is unacceptable.

Future

These recent results should eliminate some of the pessimism that has accompanied a diagnosis of Ewing's sarcoma. Unless there is a local team of orthopedic, radiotherapeutic, and medical or pediatric physicians available with the expertise in caring for a patient with Ewing's sarcoma, these patients should be handled at a large referral center. There is a continued need to improve the management of these patients and future improvement in survival for this tumor depends on clinical trials to optimize multi-agent chemotherapy, and better delineation of the most beneficial treatment for the primary tumor that causes the least long term complications.

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Adjuvant Therapy of Malignant Melanoma

GERALD J. VOSIKA, M.D.*

MALIGNANT MELANOMA of the skin, although usually amenable to initial surgical therapy, will eventually reoccur in 50% of the patients. Despite second line therapy, these patients invariably succumb to their disease. The uniformly poor prognosis attending recurrence of the disease has prompted clinical trials of adjuvant therapy. The use of such surgical adjuvant modalities is based in part, on the ability to recognize the patient at high risk for development of subsequent disease. Adjuvant procedures which have been used include prophylactic lymph node dissection, arterial perfusion, chemotherapy and/or immunotherapy.

Natural History and Risk Factors

A number of factors have been related to the natural history and probability of recurrence following initial surgical treatment for malignant melanoma. One of the major determinants is the type and depth of the initial lesion. Malignant melanoma typically grows in an orderly fashion. Initially it undergoes a horizontal or radial growth phase. During this period of time, the lesion is confined to the epidermis. Later, the lesion assumes a vertical growth phase and penetrates into the dermis and subdermis. The prognosis is directly related to the vertical depth of the lesion. On the basis of their location and growth patterns, three types of melanoma are recognized. Lentigo malignant melanoma is an indolent disease which usually occurs on the face and neck of older (50 to 70 years) individuals. It has a long (10 to 15 years) radical growth phase before becoming invasive. Superficial spreading melanoma occurs anywhere on the body. Its radial growth phase is usually less than five years after which vertical growth occurs. Nodular melanoma has essentially no radial growth phase but almost from its beginning assumes a vertical growth into the dermis

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and subcutaneous tissue. These three lesions differ in their prognosis by virtue of the fact that they differ in the frequency that they are found to invade the dermis and subcutaneous tissue.

Several systems are utilized to classify lesions according to their depth. The most frequently utilized are "Clark's Levels" and "Breslow's Depth." Clark devised a system of classifying melanomas by their depth into 1 to 5 levels. Level 1 is carcinoma in situ. Level 2 is a lesion confined to the papillary dermis. Level 3 lesions penetrate up to the reticular dermis. Level 4 goes into the reticular dermis. Level 5 penetrates the subcutaneous tissue. Breslow classified melanomas by their depth in mm. The probability of recurrence is directly related to the depth of the lesion being greater than 50% for a Clark's Level IV lesion or one with a depth of 2.5 mm or more.

Other independent factors which influence the prognosis are the location of the primary lesion, the status of regional nodes, age and sex. However. the main factor influencing the use of adjuvant therapy is the depth of the lesion and the status of the regional lymph nodes. Most institutions studying the disease consider anyone with a level 4 lesion or Stage II disease (lymph nodes involved) a candidate for adjuvant therapy.

Node Dissection

Considerable controversy surrounds the use of "prophylactic" regional node dissection for clinically negative nodes. Patients with a Clark's Level III or greater lesion have a 20% chance of having microscopic lymph node metastasis. Thus, the rationale for node dissection. While the approach may seem logical, several authors have questioned the advantage in terms of end results. Although randomized trials may show no difference between prophylactic and therapeutic node dissection, the multiple prognostic factors in melanoma make it difficult to obtain balanced study groups. Since the incidence of distant metastases increases with the depth of the lesion, node dissection may salvage only a small percent of the cases. This may be difficult to show in randomized therapy.

Chemotherapy

Two controlled prospective randomized studies have appeared utilizing adjuvant chemotherapy. The Central Oncology Group randomized between February 1972 and February 1974, 174 patients with surgically resectable high risk Stage I, Stage II, or Stage III disease to receive either no therapy or 4 courses of Imidazole carboxamide 4.5 mg//kg/d for 10 days in a 12 month period post operative. DTIC, as administered, was not apparently beneficial ($p > 0.04$) and may have been harmful as the recurrence and death rates were both slightly higher in the DTIC treated group. Data relative to the comparative characteristics of the two groups is not available.

A recently published study of adjuvant chemotherapy randomized patients with clinical Stage I, Clark's Level III to IV to one of three possible treatment arms. Patients with melanomas were randomized to either no further therapy, systemic chemotherapy or regional intraarterial chemotherapy and systemic therapy. Patients with trunk lesion or those who could not undergo intraarterial infusion were randomized to no further therapy or systemic chemotherapy. Primary surgical therapy was excision to 4cm in all directions and down to the deep facia followed by split thickness skin graft.

Systemic chemotherapy was begun one month after surgery and consisted of procarbazine (30mg/m^2/d x 7), Vinblastine (6mg/m^2 on day one only), thiotepa (6mg/m^2 on day 2), rufocromycin (60 ug/m^2 on day one) and methotrexate (15 mg/m^2 on day one). The courses were repeated every two weeks for 3 months, then every four weeks to 18 months.

Intraarterial (IA) chemotherapy was given prior to definative surgery and consisted of vincristine 1 mg/m^2/IA on day one and 10, and DTIC 80 mg/m^2 IA daily on day four through eight and 14 through 18. Surgery was done four weeks after the end of the IA infusion. Following surgery, patients were then placed on systemic chemotherapy. Overall, 52 (84%) of 62 patients in the chemotherapy group remained free of disease compared to 36 (65%) of 55 in the control group ($p > 0.05$). When evaluated in terms of know prognostic factors, it was found that while adjuvant therapy had no apparent effect on the relapse rate in the female, significant effect was observed in males. This was felt due to the better prognosis of women with melanoma. This benefit for the male was most pronounced with extremity lesions and less so for trunk lesions. No toxicity data was given. Maximum follow-up is three years although the median is less than two. Whether these figures persist with time will be of interest in noting if a delay in recurrence or perhaps increased cure rate was achieved. The authors have interpreted the results cautiously suggesting that "this form of chemotherapy may be of some use in prolonging disease free survival." This excellent report should stimulate additional studies to verify the conclusions. It should be noted that the chemotherapy in this study was considerably more intense than the

COG study of adjuvant DTIC.

Limb Perfusion

The use of isolated extracorporal perfusion for recurrent extremity melanoma was first described in 1958 by Cheech et al. They found phenylalanine mustard to be an effective agent. The practice of isolated perfusion as a part of the initial treatment of extremity melanoma has subsequently been used extensively at the M.D. Anderson Hospital. Their results have been updated and reported by several authors over the past 20 years. The most recent article by Sugarbalar et al. gives the results for 199 patients seen between 1958 and 1969. These patients all had pathological Stage I Clark's Level III to V disease. All patients had deep lymph node removal prior to the perfusion. Patients who had pathological Stage II disease were excluded from this particular tabulation. Patients with lesion outside the effective perfusion zone were also excluded.

Of 197 patients determinate for five years 148 (75%) remained free of disease. Actuarial non-failure rates at 2, 5, and seven years were 87.9, 77.8 and 75%. Males with lower extremity lesions were noted to have the poorest prognosis. These results were better than historical control cases. The use of historical controls always raises a problem with such studies especially since comparable results have been obtained with surgery alone.

Immunotherapy

The literature is overwhelmed (approximately 100 articles) with pilot type, non-randomized, uncontrolled phase II studies of all sorts of adjuvant immunotherapy for patients with malignant melanoma. Four studies deserve mention. The first is a study done at the M.D. Anderson Hospital using BCG by scarification. This was the first major study reported. It utilized historical controls and therefore is open to question. It reported, of course, improved survival and decreased recurrence in patients receiving BCG following surgical treatment of Stage II disease. A similar but prospectively randomized study was done by a second institution using the same strain of BCG at a somewhat lower dose. They observed no difference in the treated group when compared to the randomized controls. It is of note, however, that the treated group did do better than a historical control group.

An initial non-randomized study at UCLA reported encouraging results. Preliminary results of a subsequent randomized study still in progress supports the earlier positive results. Finally, the World Health Organization is sponsoring an adjuvant study in which patients are randomized to either no treatment, DTIC, BCG, or both. Preliminary results indicate that all treatment arms are doing better than controls. Detailed final analysis of this study with regard to the adequacy of the randomization is awaited with interest.

Summary

Definite recommendations are not possible. Despite some evidence to the contrary, most surgeons prefer node dissection for patients with a poor prognosis. Current studies utilizing chemotherapy and/or immunotherapy appear promising. Final results are needed. Patients should be, if possible, entered in a study protocol of adjuvant therapy so that these questions can be answered.

New Officers for 1979-1980

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Lung Cancer
Current Evaluation and Therapy

GERALD VOSIKA, M.D.*

LUNG CANCER, an epidemic disease, is the most frequent malignancy in the United States male population. In the female population, there has been a rapid increase in the incidence of lung cancer since 1960. If this continues, it will soon exceed the incidence of breast cancer. When both sexes are considered, lung cancer had an incidence of 39 per 100,000 in 1969 compared to 44 per 100,000 for colon and rectal carcinoma, and 42 per 100,000 for breast cancer.

Lung cancer denotes a group of at least 5 separate diseases. The natural history and management of these patients depends upon the histological type. Squamous cell carcinoma (epidermoid carcinoma) accounts for approximately 40% of all cases. It usually remains localized to the chest and metastasizes only late in its course. It is the type most frequently amendable to surgical therapy. Adenocarcinoma accounts for approximately 20% of cases of lung cancer. It is most frequently peripheral in location. Approximately 50% of patients will have distant metastasis at diagnosis. Only 20% will be resectable. Large cell carcinoma accounts for approximately 15% of cases of lung cancer. Like adenocarcinoma, it is frequently peripheral. The tumor itself is usually very large and also frequently metastasized early.

Alveolar cell carcinoma is an uncommon malignancy usually grouped under adenocarcinoma. It is, however, a separate entity in its clinical behavior. It frequently is resectable early in its course, but reoccurs in multiple location. It is frequently very slowly progressive and responds well to chemotherapy. Small cell undifferentiated carcinoma represents approximately 20% of all lung cancer. It is the most malignant of all lung cancer. It is by virtue of its cell type considered to be metastatic at diagnosis. The median survival, untreated, is two to four months. It is not a surgical disease.

The evaluation of the patient with lung cancer depends in part on the apparent resectability of the initial lesion. In the absence of signs or symptoms, an extensive evaluation for distant metastasis is positive in only approximately 5% of patients. Therefore, a "routine" metastatic workup is not indicated in evaluating a patient for surgery. A mediastinoscopy prior to thoractomy is helpful in that small cell carcinoma is frequently metastatic to the mediastinal nodes. Additionally, in the absence of mediastinal disease, approximately 80% of patients with an appropriate lesion will be resectable for cure.

Several staging systems for lung cancer are currently being utilized. The TNM system has been used mostly in squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The Veterans Administration system of limited and extensive disease has been most frequently applied to the patients with small cell undifferentiated carcinoma.

Surgical Therapy

Surgery remains the only definitive therapy in patients with Stage I or II squamous cell carcinoma, adenocarcinoma or large cell carcinoma. Surgery, with some exceptions, is not usually felt to be contraindicated in patients with Stage III disease and/or mediastinal involvement. Exceptions include: localized disease with chest wall invasion; squamous cell or large cell carcinoma with low ipsilateral or subcarinal involvement; and a patient with the superior sulcus syndrome on Pancoast tumor. In the later instance, cure has been achieved with the combination of surgery and irradiation therapy.

Five year survival rate for patients undergoing surgical therapy are 40 to 55% for Stage I disease, 25-30% for Stage II, and usually less than 10% for Stage III disease. The highest cure rates are in patients with squamous cell carcinoma since this is more frequently a localized disease.

Surgical therapy is contraindicated in patients with small cell undifferentiated carcinoma since this is metastatic in essentially all patients at diagnosis.

Adjuvant Therapy in Non-Oat Cell Carcinoma

Adjuvant radiation therapy has been utilized in several controlled and non-controlled studies. When.

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stratified for cell type and stage of disease, there is evidence of real benefit in patients with resectable gross nodal involvement.

Both single agent and combination adjuvant chemotherapy programs have been and are currently being evaluated. Nitrogen mustard, long term low dose cyclophosphamide, high dose cyclophosphamide, cyclophosphamide plus busulfan, and CCNU plus hydrea have all shown no benefit. A single positive study employing mitomycin C plus Chromycin A_3 has appeared. No reports utilizing adriamycin have appeared.

Adjuvant immunotherapy has had the most encouraging results in lung cancer to date. Two drugs are of note. The use of intrapleural BCG has been found to be of significant benefit in patients with Stage I but not Stage II or III disease. In related studies, an apparent beneficial effect of vaccination with autologous tumor cells and Conconavalin A or with purified tumor antigen, both of which were given in Freund's complete adjuvant, has been reported.

Levamisol, an antihelminthic which increases T cell function, has been studied in a randomized trail. A significant benefit was shown for patients who weighed less than 70 kilogram and therefore received an "adequate" dose of the drug. This interesting study needs to be repeated using drug doses based on a weight or body surface basis.

Chemotherapy Small Cell Carcinoma

Major chemotherapeutic advances have occurred in the treatment of patients with small cell undifferentiated carcinoma of the lung. Data from a Veterans Administration Lung Cancer Study first demonstrated the sensitivity of this disease to cyclophosphamide. Subsequently, numerous studies have demonstrated the sensitivity of small cell carcinoma to a variety of agents.

The current approach to the patient with small cell carcinoma should include a thorough evaluation to define the extent of disease. This should include radionucleotide evaluation of liver and bones as well as a bone marrow examination. Patients with limited disease, i.e., disease confined to one hemithorax, have a better prognosis than those with disseminated disease.

All patients with small cell carcinoma should be initially treated with combination chemotherapies. Although the optimal combinations are unknown, most programs utilize three or four different drugs. Drugs commonly employed are cyclophosphamide, adriamycin, methotrexate, a nitrosourea, vincristine, and procarbazine. The objective response rate for patients with limited disease usually exceeds 80%. At least 50% of patients with limited disease have a complete response. The response rates are less for patients with extensive disease. Currently, vigorous therapy has increased the median survival in patients with small cell carcinoma from 3 months to greater than 1 year. The role of irradiation therapy is currently undefined. Some studies utilize irradiation to the primary lesion along with chemotherapy. Although this increases the complete response rate, it does not necessarily translate into increased longevity. Since small cell carcinoma is sensitive to irradiation and since occasional cures by this modality occur, it seems reasonable to utilize it in patients with limited disease following an initial response to chemotherapy.

The use of prophylactic whole brain irradiation is also controversial. While it does prevent the occurrence of brain metastasis, it has not prolonged survival, because patients die of disseminated disease. Thus, irradiation of sanctuaries or occult metastasis is not beneficial in the absence of effective systemic chemotherapy. Almost all therapy programs currently utilized are outpatient regimens. The NIH is evaluating a program which results in severe bone marrow suppression. While this may prove to be necessary in some patients with extensive disease, it is not needed in patients with limited disease. Small cell carcinoma is a potentially curable disease. All patients deserve vigorous chemotherapy.

Although small cell carcinoma is not a surgical disease, surgical debulking may play a real role in the future management of this problem. Patients who have had lobectomies inadvertently followed by chemotherapy have done quite well.

Non-Small Cell Carcinoma

Although less dramatic, increased response rates and survival are being reported for patients with non-small cell carcinoma of the lung. This is particularly true in patients with large cell carcinoma and adenocarcinoma where response rates of 50% have been achieved with the two drug combination of CCNU and adriamycin, and with a four drug MACC combination of CCNU, adriamycin, cytoxan and methotrexate. Complete response have been achieved with significant prolongation of life. Although squamous cell carcinoma is more resistant to therapy, responses in 46% of patients have been reported utilizing CAMP, a combination of cyclophosphamide, adriamycin, methotrexate and procarbazine. The complete response role is currently quite modest (approximately 25%) in these patients.

Patients who respond live longer than non-responders such that early combination therapy is warranted. The most important single agent is adriamycin with reported response rates up to 40% in non-small cell carcinoma.

Summary

Only several years ago, chemotherapy of lung cancer was considered palliative. Frequently it was considered worse than the disease. The old question "does response improve survival" was frequently asked. The current results not only justify treatment but warrant a vigorous approach to the problem.

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Advanced Breast Cancer

Current Therapy

DAVID T. KIANG, M.D., PH.D.*

Chemotherapy

Single agents, such as cyclophosphamide, 5-fluorouracil or Methotrexate yielded a response rate in disseminated breast cancer of 24-40%. A combination of four agents (cyclophosphamide, 5-fluorouracil, Methotrexate and Vincristine) produced an average response rate of 57%. Although earlier study of the five drug regimen (above four agents plus prednisone) by Cooper reported a response rate of 88%, subsequent studies on large numbers of patients demonstrated a response rate in the range of 42-68%. Adriamycin, the most effective chemotherapy agent against breast cancer, was lately introduced and was found more effective when used as the induction agent. The combinations of chemotherapy used currently are: (A) cyclophosphamide, Methotrexate, 5-FU, Vincristine and prednisone;[1] (B) cyclophosphamide, Methotrexate, 5-FU (CMF);[1] (C) Adriamycin and cyclophosphamide;[2] and (D) cyclophosphamide, Adriamycin, 5-FU (CAF).[3] However, no matter which combination being used, the response rate has reached plateau at 50-60% with a median duration of response around eight months.

Side effects from most combination chemotherapy, although tolerable, are not pleasant and sometimes drastic. The effectiveness of secondary chemotherapy after initial combination chemotherapy is usually limited.

Hormonal Therapy

Prior to the availability of estrogen receptor assay, the response rate of breast cancer to endocrine therapy, either by surgery or additive hormones, was 30%. Knowing that the tumor is receptor negative will save the patient from unnecessary ablative surgery and also save the time usually spent for observation of the response to hormonal therapy. In the estrogen receptor positive group, the response rate is 60%. In the premenopausal patient, oophorectomy should be the first choice of therapy. Although a combination of oophorectomy and adrenalectomy provide a higher response rate, the overall survival in comparison with oophorectomy followed by adrenalectomy was essentially unchanged.[4] For the postmenopausal group (four years or over), additive hormonal therapy such as estrogen or anti-estrogen could be used. Tumors developed or recurred in the paramenopausal phase are usually receptor negative; only 11% of them contain a significant amount of estrogen receptors. The effect of hormone therapy for paramenopausal tumors is therefore frequently unsatisfactory.[5]

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Unlike chemotherapy, secondary hormone therapy in a previous hormonal responder yields a response rate of around 60-80%. Sequential hormonal therapy should be fully utilized to obtain maximal favorable results. Patients who responded to estrogen therapy occasionally also respond to hormonal withdrawal at the time of relapse.

Anti-Hormone Therapy

The two anti-estrogens which are currently used for the treatment of breast cancer are nafoxidine and tamoxifen.[6] These are triphenylethylene derivatives with the ability to bind to estrogen receptors. Most patients treated with tamoxifen, 20 mg. b.i.d. are postmenopausal. The rate of objective response in various studies has ranged from 22-49%. Tumors containing estrogen receptors and those that responded to previous hormonal manipulation tended to respond to tamoxifen (60% and 69% respectively.)[7] The average median duration of the response lasts approximately 9-11+ months. Objective response of advanced breast cancer to tamoxifen has been observed in patients who had hypophysectomy or adrenalectomy. Therefore, the anti-tumor effects of tamoxifen is directly on the tumor cells rather than indirectly via the pituitary-gonadal or adrenal-gonadal axis.

The anti-tumor effect of nafoxidine is comparable to tamoxifen; while the side effects are somewhat undesirable. Dryness of the skin, loss of hair and the light sensitivity of the skin are frequently observed from nafoxidine and are less tolerable. However, the side effects from tamoxifen are usually mild and well tolerated, including nausea, vomiting, hot flashes, lightheadedness, vaginal bleeding and occasional transient thrombocytopenia.

Aminoglutethimide is a potent agent blocking the conversion of cholesterol to pregnenolone in the adrenal gland and therefore suppresses the production of androgens, estrogens, and aldosterone. The response rate in patients treated with the combination of aminoglutethimide (1 gram) and hydrocortisone (40 mg.) daily was 38%.[8] The median duration of the response was 12+ months. These results are comparable to that from surgical adrenalectomy. The main side effects, skin flushes and lethargy, occurred during the first few weeks of therapy and are well tolerated.

Combination Therapy

Evidence is now accumulated to suggest that breast cancers are heterogeneous in cell types. The tumor is composed of hormonal dependent and/or independent cells, and of chemotherapy sensitive and/or insensitive cells in various combinations. Therefore, a combination of hormone and chemotherapy has been advocated. Some encouraging results were available that early chemotherapy following oophorectomy in premenopausal patients offered an improved, *but not statistically significant,* response rate, duration of response, and survival over that of oophorectomy followed by late chemotherapy at the time of progressive disease.

Combinations of various types of endocrine therapy have not been extensively studied. This is largely due to a poor understanding of the mechanism of additive hormone in the suppression of the tumor growth, and also attributed to the complexity of the interaction among hormones. Combinations of estrogen and progesterone, or of anti-estrogen and androgen were reported to have a higher response rate than each agent used alone. However, a combination of anti-estrogen and oophorectomy may not be advisable. In some instances, anti-estrogen reduces tumor suppression from oophorectomy. The mild estrogenic property of anti-estrogens may be responsible for this adverse effect.

Strategy in Management

Choice of appropriate therapy for disseminated breast cancer should be based on the following factors: (A) Tumor estrogen receptor; (B) Extent of the disease; (C) Rate of disease progression and; (D) Tolerance to chemotherapy. When a rapid control of the growth of the cancer is indicated, or the result of the tumor estrogen receptor is negative, combination chemotherapy should be the choice. In a slowly growing tumor, hormonal therapy could be tried, especially when the tumor is positive for estrogen receptors. Radiation therapy to a local lesion for palliative purposes and supportive therapies should be considered along the entire course of the disease.

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Advanced Testis Cancer

B. J. KENNEDY, M.D.*

THE GREATEST PROGRESS in attaining cure of advanced cancer has been attained in testis cancer. By a concerted effort in early detection, definitive initial therapy, and effective chemotherapy, this disease should become curable in most instances.

Staging of testis cancer is essential in the management of this tumor. The staging procedure requires a careful physical examination and liver function tests. Retroperitoneal disease can be demonstrated by appropriate intravenous pyelograms, lymphangiogram, sonogram and/or computerized tomography. The detection of distant disease involves chest roentgenogram, lung tomography and liver scan. Brain scans are not necessary in asymptomatic patients. The biologic markers (alpha-fetoprotein, lactic dehydrogenase, and beta subunit of human chorionic gonadotrophin) are measured before orchiectomy, following orchiectomy and following lymphadenectomy[1] (see report in this issue on the use of biologic markers for the entire course of the disease.†).

Stage I testis cancer is disease limited to the testis. Stage II disease involves the retroperitoneal lymph nodes, but not involving the abdominal viscera, with no disease above the diaphragm. Stage III disease is beyond the retroperitoneal regional lymph nodes or disease present above the diaphragm.

Inguinal orchiectomy is the only approved surgical procedure for the initial treatment of testis cancer. For a true Stage I disease cure should be accomplished in over 95% of patients. Radical retroperitoneal lymphadenectomy in non-seminomatous tumors provides a > 60% three year survival without recurrence. A 75% three year survival is reported with combined radiotherapy and surgical lymphadenectomy. For pure seminoma, radiotherapy provides a cure rate in Stages I and II of at least 96%. Chemotherapy is employed in the management of Stage III testicular neoplasms regardless of histology.

The histology of testicular cancer is an important part of tumor management. The common tumor types are seminoma, embryonal cell carcinoma, teratocarcinoma, teratoma, choriocarcinoma, and yolk sac tumor. Combinations of these exist. It is important that the testis removed at orchiectomy be sampled in multiple areas in order to have a fair assessment of the primary tumor histology. Biopsy of distant metastases also is helpful in establishing the histologic nature of disseminated disease.

The progress in the chemotherapy of advanced testis cancer has been outstanding. Initially, Li and Hertz employing triple therapy (chlorambucil, methotrexate and dactinomycin) demonstrated that complete regressions could be produced in 13% of patients, for more than nine months. The active agent in this regimen was the Dactinomycin. This was the most common therapy employed during the 50s. In the 60s mithramycin was demonstrated to be effective in embryonal cell carcinoma of the testis. This agent proved to be specific for embryonal cell carcinoma of the testis.[2] For those patients undergoing complete regression lasting for one year, none have recurred. It became apparent that cure of advanced cancer might be attainable by chemotherapy (Table).

Subsequently, the combinations of vinblastine and bleomycin, especially by infusion of bleomycin, increased the complete remission rate to 40%. In the past three years, the reports of combination chemotherapy involving vinblastine, bleomycin and cis-diamminedichloroplatinum have produced complete and partial remissions in 100% of patients. Emphasis has been made on treating patients early.[3] Complete regression rates have become the only important figure. It is in this category that cure will be attained. Although complete remission rates of 70-85% are being reported, the interval of freedom from disease is frequently less than two years. It is desirable that a two year follow up of the result of chemotherapy be attained before reporting a complete remission. Under this circumstance, at least 55% of patients with stage III testis cancer are free of disease.

Using a modification of the VBP regimen we have attained a complete remission rate of 89% with a follow-up of 12 + months, suggesting that continued study of these treatment systems will produce results closer to the total cure rate.

Following orchiectomy, the results from surgery and radiotherapy demonstrated that most recurrences occurred within the first two years after orchiectomy. At the end of three years, the mortality of patients in

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†See page 507.

TABLE

Complete Regression Rates for Chemotherapy in Advanced Testis Cancer

Investigator	Year	Chemotherapy	% Complete Regression
Li	1960	Dactinomycin Methotrexate, Chlorambucil	13
McKenzie	1966	Dactinomycin	14
Kennedy	1970	Mithramycin	22
Samuels	1973	Vinblastine + intermittent bleomycin	32
Samuels	1975	Vinblastine + bleomycin infusion	40
Golbey	1977	VAB III	62
Einhorn	1977	Vinblastine, bleomycin + cis-platinum infusion	70

this age group with this disease equals that of men without cancer of the testis.[4] Hence, it would appear that patients with stage III disease with no evidence of tumor two years after chemotherapy also have an exceptional chance to be cured by chemotherapy. Compared to the fact that 15 years ago 85% of patients with embryonal cell cancer were dead within two years of detection, the progress with chemotherapy is phenomenal.

The current management of advanced testis cancer requires careful assessment of the total disease and the continuous use of the biologic markers to monitor the recurrence and response to treatment. Two programs of chemotherapy are in use: the VAB IV program of Golbey employs vinblastine, Adriamycin, bleomycin, dactinomycin and cis-platinum. Although a somewhat complicated schedule, the toxicity is reported to be low. The combination of vinblastine, bleomycin and cis-platinum initiated by Einhorn is more toxic, but may have a slightly greater complete remission rate. Modification of doses are being studied. Adequate support facilities are required for these treatments which should be administered by those skilled in the use of these agents. The initial chemotherapy treatment of this disease is the only time that cure can be attained. Failure to utilize the maximal therapy may result in not attaining a complete regression. A second attempt at chemotherapy usually cannot attain a complete regression and death is assured.

Because of the progress in stage III testis cancer, and because early stage III testis cancer responds more adequately than late disease, the use of chemotherapy in stage II testis cancer is being investigated as an adjuvant to surgery. Although surgery plus radiotherapy can obtain about 80% three year survivals without recurrence, 20% of patients will recur. Adjuvant chemotherapy will attempt to cure the remaining group. Clinical studies are underway. Adjuvant chemotherapy probably must be the same maximal dose schedule as employed in the therapy of advanced disease. Presumably, doses or agents employed less than optimally will fail to attain cure.

It is apparent that young men are not aware of testis cancer as an entity. Vigorous public education is necessary to encourage early consultations with a physician. With optimal physician recognition of testis cancer, early detection is feasible. The ultimate projected goal in the management of nonseminomatous testis cancer is early inguinal orchiectomy, adequate clinical staging, effective use of the biologic markers and optimal chemotherapy. Clinical investigations will lead towards this direction.

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Advanced Ovarian Cancer

B. J. KENNEDY, M.D.*

CARCINOMA OF THE OVARY is a challenging disease for gynecologic oncologists. In this past year, 17,000 women developed ovarian cancer and it was estimated that 70% would die of this disease. Approximately 60-70% of ovarian cancers, when diagnosed, will be at the advanced stages III and IV. When diagnosed as stage I, the five year cure rate approaches 90% when surgery is followed by radiation therapy or adjuvant chemotherapy.

Stage I ovarian cancer is growth limited to the ovaries with subdivisions for the presence of ascites, positive peritoneal washings and integrity of the ovarian capsule. It is important to emphasize that in stage I with disease limited to the ovaries, the presence of positive peritoneal washings is not an adverse sign. In stage II cancer, growth has extended to other organs within the pelvis. In stage III, the tumors extend out of the pelvis, but are still intra-abdominal. Stage IV tumors have metastasized to the liver and/or outside the abdominal cavity. Unfortunately, ovarian cancer is not often detected in the early phase, with more than one-half of the patients having disease outside the pelvis.

Surgery usually involves total abdominal hysterectomy and bilateral salpingoophorectomy. Some physicians remove the omentum which is a source of microscopic deposits. When surgery cannot be complete, reduction of the bulk tumor is worthwhile. This provides improved well being and sufficient time to administer chemotherapy.

For advanced stage III and IV disease, chemotherapy appears to be the preferred method of management. Studies with radiotherapy prior to chemotherapy increases the hazards of myelosuppression from chemotherapy. The converse is also true in that patients initially managed with chemotherapy are not able to tolerate large doses of radiotherapy subsequently.

The introduction of the alkylating agents produced response rates in advanced ovarian cancer ranging from 25-45%. Those patients who respond have a median survival over three times that of the non-responders.

Recent chemotherapy studies have demonstrated further progress with encouraging results in trials with new drug combinations. Hexamethylmelamine, cyclophosphamide, methotrexate, and 5-FU (Hexa-CAF) has yielded an overall response rate of 76% compared with a 54% in L-PAM (Melphalan) treated patients with stage III disease. This combination produced 33% complete responses and a survival rate twice that of the single agent.

The Hexa-CAF schedule, 600 mg/m^2 of 5-FU and 40 mg/m^2 of methotrexate, both intravenously in day 1 and 8 and oral administration of 150 mg/m^2 each of hexamethylmelamine and cyclophosphamide daily from day 1 through day 14, results in depression of the immune system and bone marrow. After two weeks recovery, the cycles are repeated for six months.

Other studies employing two-drug combinations have revealed responses greater than the single agent. In patients previously treated with alkylating agents, upon reactivation of the disease, the two-drug combination of Adriamycin and cis-platinum has been beneficial. Complete remissions were attained in 4 patients of 24 treated wtih duration of control up to one year. Examination with the fiberoptic tube is a useful means to demonstrate residual disease, especially in patients who have undergone a complete clinical regression. This technique avoids the need for surgical "second-look" procedures. Furthermore, the demonstration of residual disease reinforces the need for continuing vigorous therapy, rather than a maintenance program. Chemotherapy programs are usually continued as long as a response is demonstrated. Overall, it is apparent that the chemotherapy of ovarian cancer is making rapid strides in control of the disease. For early stages of the ovarian cancer, the use of adjuvant chemotherapy appears to be an important addition to the surgical maneuvers.

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Acute Lymphoblastic Leukemia of Childhood

PETER F. COCCIA, M.D.* and MARK E. NESBIT, JR., M.D.†

ACUTE LEUKEMIA is the most common pediatric malignancy. Over 2000 children are diagnosed annually. Approximately 80% of children with leukemia have acute lymphoblastic leukemia (ALL) and the remainder have acute myelogenous leukemia. Myelogenous leukemia in children is similar to the adult disease which is discussed in Dr. Bloomfield's article in this issue.‡ Remarkable progress has been made in the characterization and treatment of childhood ALL. In the 1960s, over 95% of children with ALL died of their disease usually within three years of diagnosis. It is expected that over 50% of children with ALL diagnosed in 1979 will be alive in continuous complete remission and off therapy in five years.

Many factors are responsible for this dramatic improvement:

1. The morphologic and cytochemical characterization of ALL as distinct from myelogenous leukemia has allowed specific therapy to be applied to each disease. More recently, subtypes of ALL and lymphoid lymphomas have been recognized[1] which may have therapeutic implications in the future.
2. The ability to induce a complete remission is a necessary first step in the control of leukemia. Combinations of Vincristine, Prednisone, and a third agent (L-asparaginase, Adriamycin, Cyclophosphamide) are successful in inducing remission in about 95% of children with ALL.
3. The occurrence of isolated leukemic relapse in the central nervous system and testes during bone marrow remission has led to the recognition of biologic sanctuaries of leukemic cells possibly unaffected by systemic chemotherapy. Presymptomatic therapy of the CNS has resulted in a marked reduction in this complication. Similar studies of early diagnosis and prophylactic therapy for testicular leukemia are in progress.
4. The ability to maintain a complete remission appears to be the most important factor in ensuring prolonged survival. The development of combinations of multiple chemotherapeutic agents has led to much longer remission durations than did the sequential use of single agents. Most children are treated with daily 6-Mercaptopurine, weekly oral Methotrexate and various other "additive" agents to maintain remission.
5. Improvements in supportive care including the recognition and appropriate treatment of metabolic complications, the development of effective antibiotics for gram negative organisms and opportunistic infections, and the ready availability of blood components (packed red blood cells, platelet and leukocyte concentrates) have led to decreased morbidity and mortality from bleeding, infection and other complications.

Prognostic Factors

Many factors have been identified which are predictive of long term survival in ALL. The most powerful predictive or prognostic factors appear to be the white blood cell (WBC) count and age at diagnosis. The lower the initial WBC, the better the chance of prolonged remission duration and survival. Similarly, children age 2-10 years at diagnosis have better prognosis than younger or older children.

Preliminary analysis of a large study undertaken by a national cooperative group, the Children's Cancer Study Group, has confirmed the importance of age at diagnosis and initial WBC. Life table analysis of remission duration of 611 children who obtained initial remission and were treated with identical chemotherapy revealed that three distinct prognostic groups could be separated on the basis of these factors:[2]

1. Low Risk: Age at diagnosis, three to seven years; WBC at diagnosis $<10{,}000$ per cu. mm. Over 90 per cent of the 175 patients in this group are in continuous complete remission at three years.
2. Average Risk: Age, three to seven years; WBC, 10,000 to 50,000 per cu. mm. Age <3 and ≥ 7; WBC $<50{,}000$ per cu. mm. About 70 per cent of the 330 patients are in remission at three years.
3. High Risk: All patients irrespective of age, WBC $>50{,}000$ per cu. mm. Of 106 patients, over 50 per cent have relapsed within 18 months of diagnosis.

Various other factors have been reported to correlate with prognosis. They include race, sex, early central nervous system involvement, extent of organomegaly and lymphadenopathy, and the presence of mass lesions, especially mediastinal enlargement. Characteristics of the leukemic blast cells; including cell surface receptors for T and B lymphocytes[3], morphologic differences, cell size, and cytochemical reactions; have also been proposed as prognostic indicators. Whether these factors have prognostic significance independent of age at diagnosis and initial WBC is being studied at present by various cooperative groups and leukemia centers.

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‡See page 529.

On the basis of the above analysis, it is clear that all children with ALL should not be treated in the same manner. Low risk patients should be treated with the least toxic effective therapy, whereas average risk patients require more intensive therapy, but the good results presently obtained in this group do not justify a radical departure from present-day therapy. In the high risk group, experimental approaches, probably with intensive multi-agent chemotherapy, will be necessary to improve remission duration and survival.

General Principles of Therapy

Detailed discussion of therapy[4] and management are beyond the scope of this article. The general strategy of therapy is similar, however, in all patients. An initial induction phase is necessary to reduce the leukemic cell population to the point that all signs and symptoms associated with leukemia disappear and normal function and hematologic status return. The finding that over 50 per cent of patients induced into and maintained in bone marrow remission for over 18 months develop central nervous system leukemia has led to routine presymptomatic or prophylactic treatment of the cranial spinal axis after remission has been successfully induced. A study by the Children's Cancer Study Group has demonstrated that cranial spinal irradiation and cranial irradiation plus intrathecal Methotrexate are equally effective in reducing the incidence of central nervous system relapse to less than 7 per cent. Intrathecal Methotrexate alone was less effective in preventing the development of this serious complication. After successful induction into remission and prophylactic central nervous system therapy is completed, it is necessary to maintain the patient on multi-agent chemotherapy for between two and five years to prevent leukemic relapse. The ideal duration of maintenance therapy is yet to be determined, but preliminary studies suggest that continuation of therapy beyond three years of continuous complete remission does not alter overall relapse rates and has the disadvantage of prolonging drug-related toxicity. It is our practice to discontinue therapy at this point if thorough investigation of the patient reveals no evidence of residual disease. About 80 per cent of patients who have therapy discontinued after 3 or more disease-free years will remain in remission indefinitely and are probably cured.

Future

Unfortunately, 40-50% of children with ALL still die of their disease or its complications. While some are remission induction failures and others die of bacterial sepsis, opportunistic infections, and bleeding; most die because of recurrence of their leukemia in the bone marrow or an extramedullary site (central nervous system and testes).

In the future, a better understanding of prognostic factors will allow the recognition of subgroups of patients with nearly 100% chance of cure with present day therapy and other biologic subtypes of ALL possibly requiring radically different types of therapy. Studies must continue to improve the outlook for patients who relapse in the bone marrow and extramedullary sites. There may be a role for bone marrow transplantation or other forms of intensive therapy in these patients. That over 50% of children with ALL can be cured today should alert all physicians to the importance of early diagnosis and to the necessity of referral to a specialized treatment center. Such centers provide the specialized laboratory resources to determine potential prognostic indicators, identify valid subtypes of ALL, and design a therapeutic program on the basis of these features. In addition, the ready availability of blood components, supportive care facilities, and highly experienced medical and paramedical personnel, are essential as part of total treatment program for childhood ALL.

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Acute Non-Lymphocytic Leukemia

CLARA D. BLOOMFIELD, M.D.*

SIGNIFICANT ADVANCES in the treatment of adult acute non-lymphocytic leukemia (ANLL) are occurring. The percentage of patients achieving complete remission (CR) is now more than 80%. The median duration of CR is more than 16 months. The number of five year disease-free survivors may be as high as 20%. It appears that some patients are being cured. These advances have greatly increased the physician's responsibility. The diagnosis of acute leukemia must be made promptly and the patient offered optimal therapy. The treatment of acute leukemia is a highly developed specialty and dependent upon sophisticated diagnostic capabilities and extensive support facilities. Consequently, patients with acute leukemia should initially be referred to specialized centers for the induction of complete remission and the development of a long range therapeutic plan.

In order to select appropriate treatment, the type of leukemia must first be determined. In some cases the diagnosis of ANLL may be established morphologically by the presence of Auer rods and classic granulation but more frequently it is necessary to cytochemically demonstrate the presence of peroxidase and/or nonspecific esterase positivity. The importance of cytochemical as well as cytologic classification has been emphasized by the recently developed French-American-British (FAB) classification, which is gaining wide spread adoption.[1] The FAB classification divides ANLL into 6 subgroups (M1-M6) based on cytology and cytochemistry. M1 is acute myeloblastic leukemia, without maturation. Differentiation from acute lymphocytic leukemia may be possible only because of peroxidase positivity. M2 is acute myeloblastic leukemia with maturation. In this type there is some differentiation of the leukemic cells into promyelocyte or myelocyte stages with the cells predominately being blasts and promyelocytes. M3 is typical hypergranular promyelocytic leukemia (APL). M4 is myelomonocytic leukemia. M5 is monocytic leukemia; it is further subdivided into a poorly differentiated and well differentiated form. M6 is erythroleukemia.

Cytogenetic analysis of the bone marrow is increasingly important in diagnosing cases of acute leukemia. About 5% of adults presenting with ANLL demonstrate the Philadelphia chromosome; these patients require a different therapeutic approach.[2] It is important to differentiate the development of ANLL from drug induced pancytopenia in patients who have been treated with cytotoxic agents or radiotherapy for other malignant or non-malignant conditions.[3] Cytogenetic analysis often establishes the diagnosis of treatment-induced ANLL since all cases reported so far have had chromosome abnormalities even when the myeloblast count was very low. Marrows from treatment induced pancytopenias usually have normal karyotypes.

The initial objective of treatment in ANLL is CR, i.e. complete disappearance of leukemic infiltrates in the bone marrow and extramedullary sites, the restoration of normal hematopoiesis and the disappearance of all signs and symptoms associated with leukemic infiltration. Remission induction for de-noveau ANLL other than M3 (APL) is readily achieved utilizing combinations which include an anthracycline antibiotic (daunorubicin or adriamycin) and continuous infusion cytosine arabinoside. With two drugs alone, approximately 67% of adults will achieve CR. The addition of 6-mercaptopurine or 6-thioguanine has boosted the CR rate to 80-85% in previously untreated patients.[4] Regimens are now available that result in CR occurring in the majority of patients after only one cycle of chemotherapy.[5]

Some forms of ANLL are more difficult to treat. Philadelphia chromosome positive (Ph^1+) ANLL appears to be relatively resistant to treatment. In addition to an anthracycline, cytosine arabinoside, 6-mercaptopurine or 6-thioguanine, vincristine and prednisone should probably be used during induction. Three or four cycles of induction therapy may be required in order to achieve CR. Treatment induced ANLL is also often resistant to currently used induction regimens, although one group has recently reported four out of five CRs.[6]

In contrast, most patients with APL (M3) will achieve CR if treated appropriately during induction. Essentially all patients with APL develop disseminated intravascular coagulation (DIC) during remission induction. When the coagulopathy is managed with continuous infusion heparin and vigorous transfusion with platelets, cryoprecipitate and fresh frozen plasma, 75% of patients will survive induction and achieve CR.[7] The only other subtype of ANLL in which a large number of patients develop DIC appears to be M5 and these patients may require management of the coagulopathy in a manner similar to that for APL. Our induction regimen for APL currently consists of daunorubicin and prednisone. When patients with APL achieve CR their remissions tend to be longer than those achieved in any other subtype of ANLL. For patients with APL our median duration of CR is currently greater than two years.

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With the development of newer more rapid induction regimens for ANLL the period of marrow hypoplasia has been decreased and the risk of fatal infection and hemorrhage reduced. Many patients now require hospitalization for only four to five weeks to achieve CR. However, most patients still require considerable blood product support as well as intensive treatment with antibiotics.

With the availability of platelet transfusions, infection has replaced hemorrhage as the most frequent cause of death during induction chemotherapy. Because overwhelming sepsis may result in rapid death, neutropenic patients undergoing induction therapy for ANLL require empiric use of broad spectrum antibiotic therapy when they become febrile. High doses of ticarcillin, cephalothin and tobramycin are frequently effective. Granulocyte transfusions may also be necessary, especially during gram negative septicemia, and the systemic use of Amphotericin may be required because of disseminated Candidiasis.

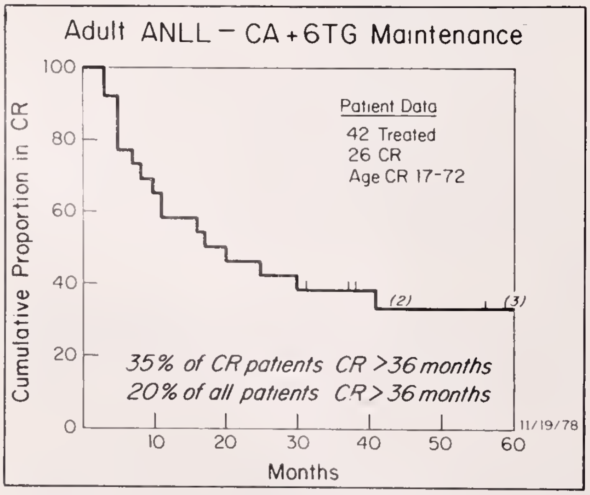

Figure — Duration of CR in patients with ANLL maintained with 6-thioguanine and cytosine arabinoside.[8] Ticks indicate patients still in remission.

Not only has the CR rate improved but the duration of remission has increased. This is probably a result both of the maintenance therapies now used and more intensive induction chemotherapy. Remissions averaging less than three months were usually reported in early studies not utilizing maintenance therapy. Recently, median maintained remission durations of greater than 15 months have been reported, frequently as a result of very intensive maintenance regimens. We have developed a simple outpatient maintenance regimen consisting of weekly oral 6-thioguanine and intramuscular cytosine arabinoside[8] which has resulted in one-third of patients remaining continuously disease free for greater than three years (Figure).

Many aspects of maintenance therapy remain controversial. It has not been clearly established that consolidation therapy is useful or necessary in conjunction with current induction regimens. Similarly, the role of late intensification therapy needs to be better defined. Currently, there is not convincing evidence that immunotherapy significantly prolongs the duration of CR. Even which patients should receive central nervous system prophylaxis is unclear. We recommend that adults with M4 or M5 ANLL, Ph^1+ ANLL and those who present with leukocyte counts of greater than 100,000 receive intrathecal cytosine arabinoside or methotrexate and cranial irradiation.

A final question regarding maintenance therapy which remains unanswered is how long it should be continued. We currently terminate maintenance therapy any time after three years that complications become apparent. A prospective randomized study is required to determine the optimal duration of maintenance therapy.

The majority of patients with ANLL who achieve CR eventually relapse. Reinduction of CR is usually possible in about 50% of patients. It appears that the initial induction regimen with the addition of one or two new drugs is optimal for achieving a second CR.[9] Occasional prolonged second CRs occur, sometimes lasting many years or indefinitely, but generally the second CR is shorter than the first. Consequently, in patients under the age of 40, at the time of their achieving their first CR, we collect and freeze bone marrow for storage. Following relapse and reinduction of CR, patients will then be able to undergo autologous transplantation, if that continues to look promising. We currently recommend allogeneic marrow transplantation, as soon as they achieve their second CR, for patients under the age of 40 who have a compatible HL-A MLC sibling. Such patients may have long term disease-free survival and possibly be cured.

Improved remission induction and maintenance regimens are resulting in more long term disease-free survivors. Five year disease-free survival is being reported in approximately 5% of patients treated by large cooperative groups. As many as 20% long term survivors have been noted by some specialized leukemia treatment centers. Data such as these suggest that some adults with ANLL are being cured.

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Acute Non-Lymphocytic Leukemia in Elderly Patients

BRUCE A. PETERSON, M.D.*

THE TREATMENT of elderly patients with acute nonlymphocytic leukemia has been a controversial subject. Published reports of therapeutic trials have focused on the success in treating younger adults while the treatment of older patients has been viewed with pessimism. Age is accepted as an important unfavorable prognostic factor. However, since nearly 40% of all patients with acute nonlymphocytic leukemia are over 60 years of age, elderly patients would stand to benefit substantially from recent therapeutic advances.[1,2].

The controversy in the past has centered around whether or not elderly patients with acute nonlymphocytic leukemia should be treated with chemotherapy at all. Unfortunately, denying these patients chemotherapy does not prevent the hemorrhagic and infectious complications which are part of the natural history of untreated leukemia. More recently, the debate has been whether or not elderly patients should be treated with the serious intent of inducing a complete remission. Clinical investigations have established that the major determinant of improved survival for patients with acute nonlymphocytic leukemia is achieving a rigidly defined complete remission. It is also recognized that only intensive therapy with multiple chemotherapeutic agents will regularly result in complete remissions.

The results of treatment with conservative therapy in elderly patients have been very disappointing. Complete remissions are rare and there is little evidence that either survival or quality of life is altered. Therapy with single agents is not recognized as being sufficient. Although peripheral leukocyte counts may be controlled for a brief while, complete remissions are obtained infrequently. Combinations of drugs that are not intensive do not yield better results. Husband et al., utilizing a multidrug program (vincristine, methotrexate, 6-mercaptopurine and prednisone) considered conservative for acute nonlymphocytic leukemia by current standards, obtained a complete remission in only one of seventeen patients (6%) over 60 years of age.[3] The median survival was only 19 days. Leukemia was thought to be the cause of death in all but two cases. The ability of elderly patients to withstand the rigors of intensive therapy has been considered. Burge et al. report only one of 20 elderly patients (5%) achieved complete remission with a therapeutic program specifically designed to reduce treatment-related morbidity and mortality.[4] Median survival was three months, but 55% of the patients died during their initial hospitalization or treatment.

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In the past, intensive therapy of acute nonlymphocytic leukemia was also of marginal benefit to elderly patients. Their ability to tolerate therapy with prolonged periods of bone marrow hypoplasia was limited and remissions were rare. Bloomfield and Theologides demonstrated in a retrospective study that elderly patients with acute nonlymphocytic leukemia could achieve complete remissions and, furthermore, these remissions were comparable in duration to those obtained by younger patients.[5] This work was confirmed by Grann et al.[6] Subsequently, we prospectively studied the same intensive multidrug regimens in patients over 60 years of age that were utilized for concurrently treated younger adults.[2] Fifty percent of patients between 60 and 70 years of age achieved complete remissions. The remission rate was not significantly different from that achieved in younger patients. For those patients over 70 years, the remission rate fell to 8%. The duration of complete remission for all elderly patients was comparable to the younger patients. The median survival for all patients 61-86 years of age was two months, but for the subgroup 61-70 years of age, the median survival was in excess of seven months. The median survival of elderly patients who achieved a complete remission was 23 months. Recently, five of eight consecutive patients (62%) over 60 years of age treated with intensive therapy have achieved complete remission. Their median age was 70 years. Significant advances in rapid remission induction with intensive chemotherapeutic regimens and supportive care have made these improvements possible.

In addition to prolonging survival, the achievement of complete remission results in an improved quality of life. Patients may continue to pursue their work or retirement activities in much the same manner that they did prior to the diagnosis of acute leukemia. There is no question that mitigating health problems frequently co-exist in the elderly patient, making intensive treatment difficult or impossible. Age is not, however, a reason to withhold treatment of the patient. As in the treatment of any illness, the patient's physical condition and personal need should be the basis for deciding therapy.

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Non-Hodgkin's Malignant Lymphoma

CLARA DERBER BLOOMFIELD, M.D.*

THE USE OF NEW diagnostic and therapeutic techniques is improving the prognosis of patients with non-Hodgkin's malignant lymphoma (NHML). Optimally managed, 70% of patients with Stage I and II disease and 20% with Stage III and IV may be cured. To achieve cure it is necessary to first correctly diagnose and classify the lymphoma, second accurately define and classify the extent of disease, and finally appropriately select therapy.[1] Long term disease-free survival is usually achieved only when appropriate radiotherapy or chemotherapy is administered as primary treatment.

The diagnostic problems in evaluating lymphoid tissue are among the most difficult in morphologic pathology. Consequently, it is important to obtain adequate tissue and prepare optimal histologic sections. A totally excised large representative node should be sent to the pathologist in the fresh state. He should make imprint or touch preparations and when feasible send a portion of fresh tissue for lymphocyte surface marker (LSM) and terminal deoxynucleotidyl transferase (TdT) assays. In difficult cases these assays may establish the diagnosis and they are often useful in determining the type of lymphoma.

Once the diagnosis of NHML is made, the tissue must be classified by an experienced hematopathologist. There are currently six major histologic classifications, those of Rappaport, Lukes and Collins, Kiel, Dorfman, the National Lymphoma Investigation and the World Health Organization. In this country the most widely used classification is that of Rappaport. There is an ongoing multi-institutional National Cancer Institute sponsored study to evaluate which histologic classification has the most clinical utility. Pending the results of that study, the Rappaport classification is probably best used since its clinical utility has been established and it is familiar to most pathologists (Table 1).

Once the diagnosis has been established and the histologic subtype determined it is necessary to define and classify (i.e. stage) the extent of disease. The Ann Arbor classification is generally used in staging NHML. This classification was developed for Hodgkin's disease and its utility in NHML remains to be established. However, since it currently is the only widely accepted system and it does assist in selecting the primary therapeutic modality, it should be used for the present.

In order to correctly classify a patient according to the Ann Arbor system, the extent of disease must be carefully evaluated. Table 2 indicates our currently recommended procedures for staging newly diagnosed patients. We shall consider some of these procedures in more detail.

Bone marrow trephine and aspiration biopsies are important early staging procedures since involvement of the marrow is the most common indication of Stage IV disease. Although the trephine biopsy is superior to aspiration for demonstrating lymphoma, aspiration is useful for cytologic classification. The optimal number of initial trephine biopsies remains to be defined. We currently recommend a single trephine biopsy for

TABLE 1

Modified Rappaport Classification

Nodular (Follicular) Lymphomas
- Lymphocytic, Poorly Differentiated (PDL-N)
- Mixed Lymphocytic-Histiocytic
- Histiocytic

Diffuse Lymphomas
- Lymphocytic, Well Differentiated (WDL-D)
- Lymphocytic, Intermediate Differentiation (IDL-D)
- Lymphocytic, Poorly Differentiated
- Mixed Lymphocytic-Histiocytic
- Histiocytic (HL-D)
- Undifferentiated, Burkitt's Type
- Undifferentiated, Pleomorphic (non-Burkitt)
- Lymphoblastic

Unclassified

TABLE 2

Staging Procedures in NHML

1. Adequate surgical biopsy
2. History and physical exam
3. Screening blood studies
4. Bone marrow biopsy
5. Chest xray ± tomograms
6. Intravenous pyelogram
7. Bone scan
8. Gastrointestinal series
9. Lymphography
10. Isotope Studies
11. Experimental non-invasive studies
12. Liver biopsy
13. Exploratory laparotomy

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newly diagnosed patients with WDL-D or IDL-D. For the other lymphomas, two biopsies should be done on one posterior iliac spine initially. If hematologic abnormalities, especially thrombocytopenia ($<140 \times 10^9/l$) or neutropenia ($<1.8 \times 10^9/l$), are present and the initial biopsies are negative, two more trephine biopsies should be performed on the opposite spine.

Postero-anterior and lateral chest films are useful in demonstrating intrathoracic adenopathy and in suggesting lung involvement with lymphoma. The radiographic picture of lung involvement is non-specific; suspect lesions should be biopsied if lymphomatous infiltration would result in a change of therapy. Mediastinal tomograms are useful in detecting minimal adenopathy. Whole lung tomograms are indicated when there are equivocal abnormalities on plain films, when there is mediastinal or hilar adenopathy and as a base line if pulmonary parenchymal lesions are present.

Intravenous pyelograms should be performed in all patients. Though they are rarely of use in staging, they reveal unsuspected ureteral obstruction in about 2% of patients. A bone scan should probably be done in the patient who has bone pain or an elevated serum alkaline phosphatase or who is Stage I or II after all staging studies except laparotomy. Bone xrays are indicated when the scan is positive. The role of the gastro-intestinal (GI) series remains to be established. A GI series should be done if there is any suggestive symptomatology.

Bipedal lymphography remains the best radiographic technique for demonstrating retroperitoneal lymphadenopathy. However, it is of limited use in the evaluation of intra-abdominal lymphadenopathy since it does not demonstrate mesenteric, splenic or portahepatic nodes nor adequately visualize nodes high in the periaortic chains. Further, in the older patient population found in NHML, the procedure is often contra-indicated since embolization of iodized oil to the lung routinely occurs and transiently impairs pulmonary function. The major indication for lymphography in NHML is if laparotomy is being considered because previous staging procedures have indicated Stage I or II disease. Under such conditions the lymphogram will identify abnormal nodes that should be biopsied.

In recent years several non-invasive staging techniques have been developed for evaluating the abdomen, including tumor specific scanning with 67 gallium citrate (^{67}Ga), ultrasonography and computerized axial tomography (CT). The contribution of these procedures to staging relative to established procedures and each other remains to be defined.

^{67}Ga is probably the best currently available tumor radionuclide. However, the accuracy and sensitivity of ^{67}Ga does not appear adequate to replace established staging procedures and tumor uptake is relatively reliable only in histiocytic lymphoma. Further, ^{67}Ga scans are expensive and time consuming and considerable irradiation is delivered to specific organs. Although ^{67}Ga scanning is occasionally useful in patients who cannot have invasive procedures, ultrasonography and CT are probably more valuable.

Ultrasonography and CT are increasingly being used in NHML for detection of mesenteric and other intra-abdominal lymph nodes not visualized by lymphography as well as for determining extranodal abdominal involvement. Comparison of the two procedures indicates that ultrasonography is considerably cheaper and that it does not deliver the ionizing radiation (1-3 rads/exam) that occurs with CT. The major problem with ultrasonography is that it is more difficult to interpret.

At the conclusion of the first 11 procedures (Table 2), almost 80% of patients will be pathologic Stage III or IV. For the remaining patients who have apparent Stage I or II disease, liver biopsy is indicated. Three types of liver biopsy may be performed: percutaneous, laparoscopic and open.[2] The usefulness of each method depends on the type of lymphoma. Current data suggest that patients with lymphocytic lymphoma should first undergo percutaneous biopsy. If that is negative, laparoscopy should be performed and if laparoscopy is negative, an open biopsy should be done. For patients with histiocytic lymphoma we recommend laparoscopy initially. If that is negative, no further liver biopsy is likely to be positive.

After the preceding staging work-up has been accomplished, there remain about 15% of patients who are Stage I or II. Laparotomy should be done if the patient will be managed differently if intra-abdominal disease is demonstrated. We currently recommend the procedure for patients for whom we are considering radiotherapy. In general, patients who pre-laparotomy have Stage I disease, remain Stage I after laparotomy. However, almost one-third of Stage II patients become Stage III or Stage IV.

Once the patient has been adequately staged, therapy can be initiated. Optimal treatment for each type of lymphoma has yet to be determined. Currently, pathologically documented Stage I and II disease of all histologies except Burkitt's lymphoma is usually treated with either extended field radiotherapy alone or limited field radiotherapy followed by adjuvant combination chemotherapy. Utilizing extended field radiotherapy alone we have found 75% of patients to remain continuously disease free for >4 years.

For patients with Stage III or IV disease, treatment depends upon the histologic subtype. We shall consider only the more frequent histologies. Optimal therapy for patients with PDL-N, is currently being hotly debated, with recommendations varying from observation alone to intensive four and five drug chemotherapy. Total body irradiation also has its proponents. The Stanford experience suggests that low dose continuous alkylating agent therapy is as effective as combination chemotherapy with cyclophosphamide-vincristine-prednisone. Our experience, and that of others, suggests that combination chemotherapy with three to five drugs increases the number of complete responders, the duration of complete remission (CR) and possibly the survival. Optimal therapy for PDL-N will probably not be determined until a number of the large multi-institutional trials that are now starting are completed.

Treatment for HL-D is less controversial. This is the one form of advanced lymphoma which appears curable with current treatment.[3] Therapy should consist of four or five drug combination chemotherapy. The regimen probably should include cyclophosphamide, adriamycin, vincristine, and prednisone with or without bleomycin or high dose methotrexate. Central nervous system involvement has increasingly been recognized in HL-D and many investigators are now directing therapy to this area, either with high dose methotrexàte or cranial irradiation with intrathecal methotrexate. With current treatment approaches about 40% of patients appear to be cured.

Diffuse lymphomas of the poorly differentiated or mixed type do poorly with current treatment regimens. Intensive multi-drug regimens appear to be required but a highly effective program has yet to be developed. Some groups are exploring the addition of total body irradiation or other forms of radiotherapy in these histologies. For Burkitt's lymphoma there is no effective treatment regimen currently available for patients with advanced disease.

The role of maintenace therapy in NHML remains to be defined. Studies comparing maintained and unmaintained patients following pathologic documentation of CR are necessary. Pathologic documentation of CR requires that all areas of initial disease be reevaluated even if this requires reexploration. It appears that in HL-D there is no advantage in continuing therapy following the induction of a CR. Among the lymphomas not now known to be curable, it is unknown whether maintenance therapy prolongs disease-free survival.

Considerable progress has been made in treating patients with NHML, but the majority of patients with advanced disease are not cured. Through careful histologic subclassification, thorough staging and pathologic documentation of complete remission following therapy better approaches to the treatment of these diseases are being developed.

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Investigational New Drugs in Cancer Chemotherapy

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WITH THE ADVENT of modern cancer chemotherapy and the subsequent wide-ranging investigations into basic and clinical pharmacology, a systematic approach to new drug development has been necessary. A major portion of the research and development of new anti-cancer drugs in the United States is organized and coordinated through programs of the National Cancer Institute. Each year many chemical compounds are screened for activity in various model tumor systems. Preclinical evaluation is undertaken in both *in vivo* animal tumors and *in vitro* cell cultures. These studies allow an assessment of anti-tumor activity against a series of standard tumor models. In addition, preliminary studies of basic pharmacology, including mechanisms of action, and toxicology are evaluated. This program of systematic preclinical screening allows the rational selection of new drugs for testing in human beings.

New drugs that are promising in preclinical evaluations are selected for advancement to clinical testing. Clinical drug trials are conducted in three phases. Phase I trials are studies of clinical pharmacology. In these studies, maximally tolerated dose, toxicity and other pharmacologic parameters are ascertained. An initial evaluation of dosage and treatment schedule is carried out. The evaluation of anti-tumor activity is not a specific goal of Phase I studies. In Phase II studies, patients with various signal types of tumors are treated with dosage schedules determined to be tolerable in Phase I. Phase II trials are done in a variety of tumors to survey for anti-tumor activity. These studies are non-random and the patients involved must have evaluable disease. If a drug shows activity against a specific tumor, it will be evaluated further. Phase III studies employ controlled clinical trials to establish or define the role of a particular new agent in cancer chemotherapy. Drugs may be studied alone or in combination. When the role of a new drug has been established, it generally becomes commercially available.

Proceeding through these various phases permits the efficient evaluation of new agents. The various steps in drug evaluation from preclinical through clinical trials are such that promising drugs may be quickly and fully evaluated, but further time and resources are not lavished on drugs that are unpromising. It is important that both the public and physicians understand and appreciate the preliminary nature of Phase I and II drug trials. The final results of these studies should not be anticipated by prematurely accepting or rejecting any claim for a given agent.

The Division of Cancer Treatment of the National Cancer Institute has, for the purpose of drug distribution, classified the investigational agents currently under its sponsorship. Three categories have been established that correlate with the availability of a drug for clinical investigation. Group A includes drugs that are undergoing preliminary evaluation. These drugs are in Phase I and early Phase II clinical trials. They are distributed under the supervision of the Division of Cancer Treatment to clinical contractors and cooperative study groups. Group B drugs are in more advanced Phase II studies. Selected drugs in this group are available through the New Drug Studies mechanism which permits affiliated investigators to utilize and study these drugs under the jurisdiction of

TABLE

Selected Investigational Drugs in Cancer Chemotherapy*

Group A	Group B
AMSA	BCG, MER-BCG
Anguidine	Dibromodulcitol
Chlorozotocin	Diglycoaldehyde
3-Deazauridine	Isophosphamide
Gallium Nitrate	Levamisole
Maytansine	High Dose Methotrexate
Neocarzinostatin	Tubercidin
PALA	VM 26
Rubidazone	VP 16-213
	Yoshi 864

Group C

Drugs	Therapeutic Indication
L-asparaginase	Acute lymphocytic leukemia
5-azacytidine	Refractory acute nonlymphocytic leukemia
Daunorubicin	Acute nonlymphocytic leukemia
Hexamethylmelamine	Ovarian carcinoma
Methyl CCNU	Carcinoma of the stomach and colon; melanoma
Streptozotocin	Islet cell carcinoma of the pancreas, carcinoid

*Adapted from the *DCT Newsletter*, January 15, 1978 (By permission.)

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comprehensive or clinical cancer centers. Finally, qualified investigators may obtain Group C drugs which although still under investigation have already established roles in specific diseases. These are drugs which have proven efficacious in multiple studies against a specific tumor and are recommended for initial or subsequent treatment. They are available for a specific clinical need. A list of selected investigational compounds currently under the sponsorship of the National Cancer Institute is presented in the Table.

One requisite for using investigational agents is that of written informed consent. The United States Food and Drug Administration requires that a patient receiving an investigational agent must be informed with regard to his treatment. Committees on the use of human subjects in research at the institution in which clinical investigation is carried out review the specific treatment protocols and consent forms. Their approval is necessary for a research program to be activated. The patient must be told the nature and purpose of the clinical investigation, possible side effects of the treatment, alternative modes of therapy and be given the opportunity to discuss in detail any questions he might have. If the patient is participating in a randomized trial, he must also be made aware of this. Every effort must be made to protect the health and the rights of the individual patient participating in clinical research.

Selected Investigational Drugs

Some of the recent developments in cancer chemotherapy are the result of new applications of established drugs. Among these is the use of extremely high doses of methotrexate.[1] High dose methotrexate represents a several hundredfold increase in dosage over standard doses and would result in inordinate toxicity if it were not possible to provide pharmacologic rescue to the normal cells. Since methotrexate is an inhibitor of dihydrofolate reductase, reduced folate when supplied to the cell after exposure to methotrexate will circumvent the major toxicities. Calcium leukovorin has been the most commonly used rescue agent. High dose methotrexate with leukovorin rescue has found clinical application in the treatment of osteogenic sarcoma and a variety of hematologic malignancies. It is also being evaluated in other types of cancer. Alternative methods of preventing toxicity and enhancing the therapeutic effects of methotrexate include the use of L-asparaginase and thymidine.

The platinum coordination complexes are among the most promising of current investigational cytotoxic compounds and represent a unique class of antineoplastic drugs.[2] Cis-diamminedichloroplatinum (II) was introduced into clinical trials in 1972 and has exhibited a remarkable degree of activity in testicular, ovarian, bladder and head and neck malignancies. The results of animal experimentation suggest that a synergistic increase in activity could be obtained when combined with Adriamycin. Extensive clinical trials combining these two agents are now in their final stages. Cis-platinum was recently made commercially available. Other heavy metal complexes are being developed with the potential for equal or improved antineoplastic activity and reduced toxicity.

Rubidazone is a new anthracycline antibiotic which has many similarities with daunorubicin and Adriamycin. In preliminary trials rubidazone has been extremely active in the treatment of refractory acute non-lymphocytic leukemia.[3,4] The toxicity observed is similar to that seen with related compounds, but it occurs at a higher dose level with rubidazone. Five-azacytidine is an anti-metabolite which also has significant activity in acute non-lymphocytic leukemia.[5] Since intensive combination chemotherapy is required to obtain complete remissions in this disease, we have initiated a pilot study employing both 5-azacytidine and rubidazone in previously treated patients with acute non-lymphocytic leukemia.

The epipodophyllotoxin derivatives, VP 16-213 and VM 26, are mitotic inhibitors which also cause a premitotic block.[6] Their precise mechanism of action is unknown. They appear to have a similar spectrum of activity, but clinical experience is currently greater with VP 16-213. VP 16-213 is active in hematologic malignancies, especially non-Hodgkin's lymphomas and acute monoblastic leukemia. A variety of solid tumors, including ovarian carcinoma and small cell carcinoma of the lung, are also responsive to VP 16-213.

There are other drugs which are also in preliminary phases of evaluation. Neocarzinostatin is a polypeptide which inhibits DNA synthesis. Patients with a wide spectrum of malignancies are currently being treated and responses have been observed in a variety of tumors including gastrointestinal and bladder carcinomas and acute leukemia. Hepatomas may be particularly responsive to neocarzinostatin. Chlorozotozin is a new nitrosourea closely related to Streptozotocin. It is hoped that this drug may have less toxicity than other similar agents. AMSA (4'-[9-acridinylamino] methanesulfon-m-anisidide) is one of a series of acridine derivatives with anti-tumor activity in preclinical tests. It is an inhibitor of DNA synthesis. Various treatment schedules have been tested and

AMSA is ready to begin early Phase II trials. PALA (phosphonoacetyl-L-aspartate) is a promising metabolic inhibitor that is entering Phase II testing.

Despite the prominent advances made in the chemotherapy of some malignancies, the majority of adult patients with metastatic cancer will certainly not be cured and may not be palliated with current therapy. Insofar as chemotherapy will continue to play a major role in the management of these patients, new drugs and more effective use of standard drugs are necessary.

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Opportunistic Infections in Patients with Cancer

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OPPORTUNISTIC INFECTIONS are a frequent complication occurring in patients with cancer and a significant cause of death. Alterations in various host defenses, anatomic barriers or immunologic response, predispose the individual to infection. These changes may result from either the tumor itself or efforts directed at diagnosing and treating the tumor. Despite the unusual nature of many opportunistic infections, recognition of predisposing conditions will permit early consideration of specific diagnoses and appropriate therapy.

Invasion, obstruction or ulceration of normal tissues by a tumor impairs anatomic or physiologic barriers to infection. For example, obstruction of a bronchus or ureter commonly results in either pneumonia or pyelonephritis, respectively. Ulcerations of skin or mucosa serve as portals of entry for microorganisms. The tumor may not only play a major role in establishing infections, but its continued presence makes treatment difficult. Chemotherapy and radiotherapy also result in physical changes which may have similar effects on susceptibility to infection. They can cause mucosal ulcerations or other effects, such as paralytic ileus, which will increase the opportunity for infection by enteric organisms.

In a similar manner, myelosuppression or alterations in the immune system may be primarily caused by either the malignancy or its treatment. Our understanding of various host defenses has increased dramatically and they are remarkable for their complexity and extent of interactions. A detailed discussion of host defenses is outside the scope of this article, but we can relate in some ways how abnormalities in these defenses caused either by malignancies or their treatment are related to specific opportunistic infections.

The neutrophil is a phagocytic cell which must travel to the site of infection to ingest the pathogen. Most chemotherapeutic agents cause a reduction in the neutrophil count. There is no serious increase in the incidence of infection until the absolute neutrophil count is below 1000-1500 cells/mm^3. However, severe infections occur frequently when the neutrophils number[1] less than 500/mm^3. In addition to quantitative changes in neutrophils, functional defects in chemotaxis and phagocytosis are induced by some drugs. This also increases the potential for infections. Neutrophil function is also impaired in some malignancies. Acute myelogenous leukemia, for example, is associated with both quantitative and qualitative defects in neutrophils. These defects are absent when the patient is in a complete remission.

Gram-negative bacterial infections are the most common life-threatening infections in neutropenic patients. A causative organism can be identified in nearly two-thirds of severely neutropenic febrile patients (>101°F). *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *E. coli* are the usual gram-negative pathogens. Staphylococcal and other gram-positive infections are occasionally seen. Prior to the empiric use of broad-spectrum antibiotic cimbinations, the median survival for these neutropenic patients was brief and the great majority died. Now with carbenicillin, gentamicin and/or cephalothin, recovery occurs in excess of 80% of patients[2,3]. The role of fixed combination trimethoprim-sulfamethoxazole, newer aminoglycosides, tobramycin and amikacin, and new synthetic penicillins, such as ticarcillin, are being evaluated. Granulocyte transfusions also aid in the treatment of infection while awaiting bone marrow recovery. However, return of sufficient numbers of functioning endogenous neutrophils is vital to the patient's survival.

Fungal superinfections commonly occur in neutropenic patients during broad-spectrum antibiotic therapy. Systemic infections, though clinically suspected, are most frequently documented at autopsy. Fungi are present in 20-30% of patients dying with acute leukemia and 10% with lymphoma. *Candida* and *Aspergillus* species, *Cryptococcus neoformans* and *Phycomycetes* are the organisms usually responsible. Newer diagnostic methods such as counter-immunoelectrophoresis aid in detecting fungal antigens. Amphotericin, with or without 5-fluorocytosine, remains the standard for treating many fungal infections[4]. Miconazole, a new and less toxic antibiotic, has proven efficacious against a variety of fungal infections.

Lymphocytes participate in both humoral and cell-mediated immunity, and functional abnormalities are associated with certain opportunistic infections.

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There are numerous subpopulations of lymphocytes which interact in complex and only partially understood manners. Despite these extensive interactions and overlap of immune function, two general classes of lymphocytes, "B" and "T" cells, can be determined by various functional and surface membrane markers. These "B" lymphocytes and "T" lymphocytes participate in humoral and cell-mediated immunity, respectively. The lymphocyte's ability to participate in the immunologic response may be impaired by either chemotherapeutic agents or by involvement with the malignant process.

Alterations in primary or secondary antibody response occur commonly in malignancies of "B" lymphocytes, such as multiple myeloma, chronic lymphocytic leukemia and some of the non-Hodgkin's lymphomas. Abnormalities in immunoglobulin production, which may result in dysgammaglobulinemia or hypogammaglobulinemia, are associated with infections caused by gram-positive bacteria, encapsulated bacteria and fungi. Gram-negative infections are becoming increasingly common.

These patients and those affected by "T" lymphocyte disorders may also be infected with *Pneumocystis carinii*. *Pneumocystis carinii* most frequently causes clinical pneumonia in patients who have recently received immunosuppressive chemotherapy, particularly corticosteroids, for lymphoproliferative malignancies. The clinical presentation may be either insidious or abrupt and rapidly progressive. The diagnosis is achieved by demonstrating the organism with methenamine silver or Giemsa stain. Very occasionally it is found in sputum. Usually, bronchial brushings and biopsy obtained through a fiberoptic bronchoscope or, in some cases, an open lung biopsy are necessary. The diagnosis is important to establish because it may be impossible to distinguish this infection clinically from other microbial infections or drug-related pulmonary diseases.

In the past, pentamidine has resulted in recovery of approximately 60% of adequately treated patients[5]. Recently, the combination of trimethoprim-sulfamethoxazole was demonstrated to be equally effective in pediatric patients[6]. It is also effective in adults. Because of the ease of administration and minimal toxicity, this combination has gained wide acceptance. Either pentamidine or trimethoprim-sulfamethoxazole may be effective in cases of pneumocystis pneumonia resistant to the other antibiotic.

A protozoan that is important in immunosuppressed patients is *Toxoplasma gondii*. Toxoplasmosis may be glandular, localized or disseminated. Neurologic manifestations predominate in over 50% of cancer patients with toxoplasmosis[7]. The diagnosis is established by demonstrating the organism in biopsy or body fluid specimens. A rising antibody titer often peaks prior to the clinical suspicion of toxoplasmosis. Under these circumstances, a very high antibody titer in a suitable clinical situation may be suggestive. An elevated IgM fluorescent antibody titer is fairly conclusive evidence of active infection. Triple sulfa therapy with pyrimethamine has been the standard treatment.

Hodgkin's disease, particularly in advanced stages, results in malfunction of "T" lymphocytes and macrophages (monocytes) which are both active in cellular immunity. The defect in macrophage function results in a propensity toward infections with intracellular bacteria including *Mycobacteria, Listeria monocytogenes* and *Salmonella* and fungal infections. Following splenectomy for staging purposes, overwhelming infections with bacteria such as *Streptococcus pneumoniae* or *Hemophilus influenzae* are seen in a small, but significant, number of patients[8]. Pneumococcal vaccine and daily oral penicillin are being tried prophylactically to prevent this syndrome which is fatal in nearly 50% of cases.

Viral infections, usually of the Herpes group, are being increasingly recognized. These infections occur in patients with lymphoma, leukemia, and advanced solid tumors receiving therapy. Herpes zoster occurs in 15-25% of patients with Hodgkin's disease. Dissemination may occur in up to 20% of those patients infected. Cytomegalovirus infections generally occur as a limited pulmonary infection in cancer patients, but fatal systemic cases are seen[9]. A documented rise in antibody titers or the observation of basophilic intranuclear inclusions in biopsy specimens aids in the diagnosis. The virus may also be cultured at times from urine and sputum. Although therapy directed specifically at the viral infection is of limited benefit, rigorous attention to clinical care and early treatment of any superinfection will allow most patients to recover from their viral infection.

Non-hematologic tumors are also associated with an impaired immunologic status, especially in advanced disease. The immunologic aberration caused by these malignancies tends to be both less specific and less profound than that associated with hematologic neoplasms. Therapy or poor nutrition, however, can enhance the impaired resistance. The degree of susceptibility to opportunistic infection usually increases with progressive disease.

Although there are a variety of factors which may predispose cancer patients to infection, the number of etiologic alternatives to be considered in an infected patient may be reduced by recognizing the immunologic and anatomic abnormalities induced in the patient and the clinical features of the suspected infection. Then, the appropriate diagnostic and therapeutic steps can be initiated early in the course of an opportunistic infection resulting in an optimal chance for success.

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Hypercalcemia in Neoplastic Diseases

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HYPERCALCEMIA IS a common complication of malignancy, particularly carcinoma of the breast and lung. Up to 40-50% of patients with metastatic breast carcinoma may develop hypercalcemia during the course of their disease. In some cases the hypercalcemia is mild and self-limiting, but in others it leads to a severe and life-threatening crisis. Other solid tumors are less frequently associated with hypercalcemia; these include kidney, bladder, cervix, esophagus, head and neck, and prostate cancers. Among the hematologic malignancies, multiple myeloma may be complicated by hypercalcemia in up to 25% of patients. Malignant lymphoma and acute leukemia are also reported causes.

This report will highlight recent fascinating investigations into the mechanisms of hypercalcemia in malignancy. We will also briefly review the clinical manifestations and the therapeutic approach to this problem.

Pathogenesis

The great majority of patients who have a malignant disease complicated by hypercalcemia have demonstrable skeletal metastases. This observation naturally led to the belief that the tumor cells within bone are mechanically disruptive causing increased resorption of bone and release of calcium into the blood. But three factors indicate that this explanation is not adequate. First, hypercalcemia may be associated with primary tumors that are still localized and not involving bone. Second, there is no obvious correlation between the degree of bone involvement and the incidence or magnitude of hypercalcemia. Third, the incidence of hypercalcemia varies considerably with the tumor cell type irrespective of the presence or absence of skeletal metastases.

Such evidence suggests that humoral effects, either local or remote, are more important than the mere presence of metastases in bone. In fact, tumors may release a variety of hormone-like substances that can affect calcium metabolism both in bone and in kidney. Such humoral substances including parathyroid hormone (PTH), the E series of prostaglandins (PGE), and osteoclast activating factor (OAF) are the putative mediators of hypercalcemia in neoplastic diseases.

Parathyroid Hormone

The combination of hypercalcemia, hypophosphatemia, and negative bone scans or surveys occurring in patients who have nonparathyroid neoplasms has been widely recognized. There are many biochemical similarities between this syndrome and primary hyperparathyroidism such as an increased serum chloride/phosphate ratio, decreased renal absorption of phosphate, and increased urinary cyclic AMP excretion. These similarities have led to the conclusion that these tumors are secreting a PTH-like substance. The syndrome is therefore termed pseudohyperparathyroidism and is associated with a variety of carcinomas, especially squamous cell carcinoma of the lung and renal cell carcinoma.

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Specific production of immunoreactive parathyroid hormone (iPTH) by tumors has been documented by several investigators. Their techniques include detecting iPTH in cancer tissue by immunofluorescence, extracting iPTH from tumor tissue, documenting arteriovenous gradients of iPTH across organs bearing the tumor, and demonstrating specific PTH production by tumor cells *in vitro*.

Most clinical reports have utilized radioimmunoassays for the measurement of circulating iPTH. Some investigators report that the serum iPTH is inappropriately elevated (either high or normal) in the majority of cancer patients with hypercalcemia[1]. In contrast, another group has reported that none of their patients with similar clinical presentations had detectable levels of serum iPTH[2]. The immunoheterogeniety of iPTH and the availability of varying anti-sera may account for the conflicting data reported in the literature. There is evidence that the serum iPTH in cancer patients may be different immunologically from native PTH. Moreover, the mere presence of iPTH in the tumors or circulation of hypercalcemic patients does not prove that these substances are active. It is conceivable that the measured iPTH may represent biologically inactive fragments.

Finally, one should keep in mind the possibility of coexisting cancer and true primary hyperparathyroidism since this has been reported frequently. Whether the association occurs more commonly than by chance is not known.

Prostaglandins

The E series of prostaglandins (PGE_1 and PGE_2) are potent stimulators of bone resorption *in vitro*. There is strong evidence to support the role of PGE_2 in the production of hypercalcemia in two animal models: mice with fibrosarcoma and rabbits with the VX2 carcinoma.

Several clinical studies suggest that PGE may also be important in cancer patients with hypercalcemia. Anecdotal reports have demonstrated that indomethacin, a potent inhibitor of prostaglandin synthetase, has reversed hypercalcemia in some patients with cancer, especially renal cell carcinoma. More elaborate studies involving measurements of plasma immunoreactive prostaglandins or a urinary metabolite of PGE (PGE-M) have presented circumstantial evidence supporting a casual role of PGE. Seyberth, et al.[3] have reported an association between elevated urinary levels of PGE-M and hypercalcemia in cancer patients. Treatment of several of these patients with indomethocin or aspirin caused a substantial fall in urinary PGE-M and a variable reduction in the serum calcium.

Osteoclast-Activating Factor (OAF)

An additional mediator of bone resorption, OAF, was first identified in 1972. This protein substance which probably exists in more than one form is secreted by lymphoid cells that have been activated by mitogens. In addition, the factor has been isolated from the supernatant fluids of short-term cultures of myeloma cells obtained by marrow aspiration in patients with multiple myeloma[4]. The secretion of this factor by myeloma cells may stimulate osteoclastic activity in adjacent bone to produce osteolytic lesions and hypercalcemia. Whether this factor has an important role in diseases other than multiple myeloma remains to be demonstrated.

Clinical Manifestations

The clinical presentation of patients with paraneoplastic hypercalcemia may vary from no symptoms at all to mild lassitude to a severe life-threatening crisis. Hypercalcemia usually affects a wide range of organ systems but may involve a particular organ system to the exclusion of others. The predominant symptoms and signs include anorexia, nausea and vomiting, constipation, lethargy, coma, dehydration, polyuria and polydipsia. But if only one organ system is involved, the physician may be misled into entertaining an incorrect diagnosis such as diabetes insipidus, stroke, or acute abdomen.

The effects of hypercalcemia on the kidney are manifold. Mild or moderate elevation of serum calcium impairs the concentrating ability of the kidney tubules leading to polyuria, polydipsia, and dehydration. More severe hypercalcemia and increasing dehydration can result in a decreased glomerular filtration rate and acute or chronic renal insufficiency. This in turn reduces the excretion of calcium and phosphorus thus setting up a ''vicious circle'' leading to the fullblown hypercalcemic crisis.

Besides the predominant symptoms discussed above, many less common manifestations may be observed. Hallucinations, psychotic behavior, hypertension, cardiac arrhythmias, peptic ulcer disease, and relapsing pancreatitis are among the many reported signs and symptoms of hypercalcemia associated with malignant disease.

Treatment

Not all cases of hypercalcemia associated with cancer demand urgent therapy. The asymptomatic patient with only mild elevation of serum calcium (less than 13 milligrams per deciliter) is best managed by specific anti-tumor therapy, by good hydration, and by avoiding immobilization.

Life-threatening hypercalcemia (e.g. serum calcium greater than 14 milligrams per deciliter or severe symptoms) is a medical emergency. The hallmark of therapy is rehydration using a saline infusion. This measure restores the depleted intravascular volume toward normal thus improving renal function. It also increases calcium excretion since sodium competitively inhibits tubular reabsorption of calcium. Furosemide can be an important adjunct in enhancing calcium excretion but must never be used in the face of an uncorrected intravascular volume deficit. Hypokalemia in particular and also hypomagnesemia are complications of hypercalcemia and its management. Deficits of these elements must be replaced vigorously.

Other useful adjuncts in the therapy of serious hypercalcemia are mithramycin and corticosteroids. Mithramycin is useful in all types of tumors since its effect is the inhibition of osteoclastic resorption activity. The recommended dose is 25 micrograms per kilogram, but lower doses may be as effective and less toxic when there is pre-existing renal impairment. Although the onset of action is relatively rapid (six to 12 hours), the maximal effect may not occur for 24-48 hours. A repeat dose may be administered in 48 hours, but too frequent administration can lead to thrombocytopenia and hepatic or renal dysfunction. Corticosteroids are most useful in managing hypercalcemia associated with breast cancer, malignant lymphoma, and multiple myeloma. The steroids are effective in part because they inhibit the growth of these tumors, but they also may antagonize the effects of vitamin D in bone.

Selected patients who have serious complicating problems such as congestive heart failure or renal failure should be considered for peritoneal or hemodialysis with a calcium-free dialyzate. Not all patients are candidates for such aggressive therapy but in certain individuals who have a recently diagnosed malignancy and have not had an adequate chemotherapeutic trial, dialysis may be life-saving.

Less useful treatment modalities are intravenous phosphate infusions and calcitonin. Phosphate infusions should never be used in the face of hyperphosphatemia or renal impairment because of reported complications such as soft tissue calcification, renal cortical necrosis, and even fatal shock. Even with normal or low serum phosphorus phosphate infusion should be reserved for only the must urgent complications such as cardiac arrhythmias. The role of porcine or salmon calcitonin in managing hypercalcemia is unclear. It may have greater efficacy when excessive PTH production is suspected. But the drug is expensive and its effect usually only transient. The effect may be enhanced by concomitant administration of oral phosphates.

The longterm medical management of chronic hypercalcemia includes effective anti-tumor therapy and avoidance of immobilization or dehydration. In addition, oral phosphates and, in selected cases, corticosteroids or indomethacin may prove useful.

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Intravascular Coagulation

GEORGE J. BOSL, M.D.* and J. ROGER EDSON, M.D.†

INTRAVASCULAR ACTIVATION of coagulation is common in patients with neoplastic disease. Although the hemorrhagic manifestations of rapid intravascular coagulation (''DIC,'' ''consumption coagulopathy,'' ''defibrination syndrome'') are easy to recognize, thrombosis occurs more frequently due to slower activation of coagulation. Early recognition and treatment of intravascular clotting may minimize morbidity and mortality in the cancer patient.

Causes

Intravascular activation of coagulation is always a secondary phenomenon. Tissue injury and/or tumor necrosis with the release of thromboplastin and plasminogen activators are present in all cancer patients with activated coagulation. Spontaneous necrosis of the neoplasm, infection, surgery, and chemotherapy may all be associated with intravascular activation of coagulation and fibrinolysis.

Neoplasms commonly release thromboplastin and plasminogen activators which are the initiators of coagulation and fibrinolysis, respectively. Mucin-producing tumors, usually causing slow activation of clotting, are associated with thrombosis and non-bacterial thrombotic endocarditis (NBTE). Acute non-lymphocytic leukemias, especially acute promyelocytic leukemia (APL), may rapidly release activators of clotting and fibrinolysis and cause rapid intravascular coagulation, hemorrhage, and ''DIC.'' Prostatic cancer is also frequently associated with hemorrhagic phenomena. Other solid tumors are less frequently associated with bleeding.

Coagulation abnormalities may also be precipitated by infection. The patient with cancer is often immunocompromised and is more susceptible to severe viral, bacterial, fungal, and parasitic infections. These infections, when blood borne may lead to thrombocytopenia, with or without ''DIC'' and hemorrhage. Thus, infection should be suspected in the appropriate clinical setting and the source identified.

Coagulation homeostasis may be disturbed by the surgical and chemical treatment of the malignant disease. The association of surgical procedures with thromboembolic phenomena is well known. In patients with cancer, an even greater risk may exist since simple manipulation of the tumor can cause the release of thromboplastin. Chemotherapy occasionally causes rapid tumor destruction with sudden rapid intravascular activation of coagulation and fibrinolysis. Rapid tumor lysis is more frequent in the hematologic malignancies, but is reported in the solid tumors as well. Successful treatment of a malignancy will ultimately remove the source of activation, but serious coagulation disturbances can occur during tumor destruction.

Clinical Manifestations

The manifestations of intravascular activation of clotting range from clinically inapparent laboratory coagulation abnormalities to thrombosis to overwhelming and fatal hemorrhage. The clinical presentation depends upon the rate of intravascular activation of coagulation and fibrinolysis. Slow activation will result in thrombosis and/or embolism and rapid activation will result in a state of coagulation factor depletion which if severe enough may cause a bleeding tendency.

Thrombophlebitis is the most common presentation of intravascular clotting related to malignancy. It may involve superficial or deep veins and is often migratory. The best known example is Trousseau's Syndrome, a migratory, superficial form of thrombophlebitis. While thought to be more common in pancreatic cancer, thrombophlebitis can occur in any malignant disease[1].

Another manifestation of the slow activation of the clotting machanism is embolization. Generally, a source can be identified, but it may occur in the absence of clinically apparent thrombosis. Embolism may occur to any organ but pulmonary embolism is the most common. NBTE is also a manifestation of chronic slow activation of coagulation and should be considered in the differential diagnosis of multiple systemic emboli. NBTE may present with encephalopathy due to bilateral cerebral infarcts. Infarction within the skin, kidney, and retina is also seen.

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Hemorrhagic phenomena are less common as initial manifestations of intravascular clotting in the patient with neoplastic disease. They are the result of rapid activation of coagulation and fibrinolysis and are most commonly seen in APL and in prostatic cancer. However, they can occur with any type of malignancy. Most frequently the skin is involved with ecchymoses and failure of hemostasis following venipuncture. Intracranial hemorrhage and serious uterine, gastrointestinal and urinary bladder hemorrhage also occur.

Laboratory Evaluation

Once a disturbance of coagulation is suspected, laboratory confirmation is necessary. The most important tests of coagulation are the prothrombin time (PT), activated partial thromboplastin time (PTT), thrombin time (TT), platelet count and plasma fibrinogen concentration. With slow activation of coagulation, an elevated fibrinogen, a normal or elevated platelet count, normal or shortened PT, shortened PTT and slightly prolonged TT are commonly observed. In the patient with rapid activation, the PT, PTT, and TT may all be prolonged, the platelet count depressed and the plasma fibrinogen concentration low. The continuum that exists between rapid and slow activation of the clotting system permits much variability in the results of the individual coagulation tests. A particular test may be normal in one case and profoundly abnormal in another. In the evaluation of rapid intravascular clotting, a single platelet count or fibrinogen determination gives the status at only one point in time. Serial determinations are necessary if the evolution of abnormal coagulation is to be detected. A normal or borderline value which becomes abnormal may herald the onset of a bleeding tendency, thereby allowing prompt intervention.

Although serum FSP are commonly elevated in neoplastic disease, the presence of FSP does not help differentiate rapid from slow activation of clotting. A simple latex agglutination test is available which is easy to perform and reasonably accurate[2]. Other tests for FSP are also available but are more difficult to perform.

Other causes of bleeding tendencies and abnormal coagulation tests can be confused with an activated clotting system. Vitamin K deficiency due to antibiotic therapy or malnutrition should be excluded. Liver disease may be associated with prolonged coagulation tests as well as the presence of FSP. Deep venous thrombosis in the absence of malignancy is also a source of FSP. The paraproteins produced by multiple myeloma and lymphoma may interfere with the clotting tests. Rarely, autoimmune phenomena with thrombocytopenia and circulating coagulation inhibitors may be the cause for a bleeding tendency. Thus, a careful evaluation of the patient's entire clinical picture is essential.

Treatment

The treatment of the patient with intravascular coagulation must be individualized. Three levels of intervention may be considered: (1) treatment of the underlying condition, (2) treatment of the coagulation process with heparin, and (3) treatment of the depletion state with blood component replacement.

Intravascular coagulation in the cancer patient is always secondary to the tumor or to one of its complications. If the primary cause of intravascular coagulation is treated, then more complicated intervention may not be needed. Infection, acidosis, shock and hypoxia should be treated promptly. If the tumor is the source of activation, then anti-neoplastic therapy may be useful in eliminating the source of thromboplastin and plasminogen activator.

In some situations, treatment of the cause cannot rapidly eliminate the source of coagulation activators. At such times, heparin may be necessary. In patients with thrombophlebitis, heparin is the treatment of choice. However, some patients relapse when switched to oral anticoagulants. Although heparin is necessary in the treatment of deep venous thrombosis, its use in the hemorrhagic state remains controversial.

The bleeding patient with "DIC" presents a difficult problem. Uncontrolled rapid clotting and fibrinolysis result in coagulation factor depletion, platelet consumption and the formation of FSP which impair platelet function and fibrin formation. Heparin may be indicated to interrupt coagulation activation. If the patient with hemorrhage requires heparin, then co-existing clotting factor depletion, thrombocytopenia and hypofibrinogenemia must also be corrected. Heparin without replacement therapy with fresh frozen plasma, platelet transfusions, and cyroprecipitate will worsen the bleeding tendency. If heparin is not used in the bleeding patient, then replacement therapy alone can result in fatal thrombosis. Therefore, fresh frozen plasma, platelet transfusions, cyroprecipitate and *low dose continuous infusion* heparin should be utilized together when rapid activation and factor consumption are prominent. It should be emphasized that this approach to the management of APL in leukemia treatment centers has resulted in a change from an almost universally fatal leukemia to one that is treatable with a high percentage of long-term remissions[3]. The simultaneous use of low dose continuous infusion heparin and coagulation factor replacement in the bleeding patient allows better control over clinical bleeding problems and may be life-saving.

Summary

Intravascular activation of coagulation in the patient with cancer is a common problem. Usually, it presents as thrombosis rather than hemorrhage. Rapid recognition of the clinical manifestations is essential so that prompt treatment can be initiated to prevent complications. A cause should be sought in all cases. In those cases where the tumor is the direct cause, the best solution will be effective treatment for the underlying malignancy. The complications of malignancies, such as infection, should be treated appropriately. Deep vein thrombophlebitis and thromboembolism require the use of heparin. In patients with DIC and hemorrhage, intervention with heparin should be accompanied by factor replacement. Careful and knowledgeable medical management is essential if morbidity and mortality secondary to intravascular clotting in the cancer patient are to be minimized.

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Nutritional Management during Cancer Therapy

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AN IMPORTANT PART of the holistic management of the patient with advancing cancer is the maintenance of a good nutritional state for as long as possible. This may contribute to a sense of well-being, to a better preservation of tissue function and repair and to a higher humoral and cellular immunocompetence. It is known that malnourished cancer patients do not tolerate surgery, radiotherapy and chemotherapy as well as the ones at a better nutritional state; they have more complications and their prognosis is not as good as that of the latter group.

At the time of the initial diagnosis of cancer or of recurrence or metastasis the patient should have a nutritional evaluation which should be repeated periodically throughout the course of the disease. The nutritional history should include a description of eating habits, meal composition and food composition with an estimate of the average daily caloric intake and distribution in proteins, fat and carbohydrates. On physical examination, the body weight-height index should be recorded although it may not be a dependable index for follow-up of the patient's nutritional status due to the tendency of these patients to retain water intracellularly and extracellular while losing flesh. Other simple anthropometric measurements such as arm circumference and skinfold thickness are more dependable indices for the status of muscle mass and adipose tissue respectively.

Simple laboratory tests with nutritional relevance are the hematocrit and the serum albumin, which along with transferrin and total iron binding capacity reflect the state of the visceral protein. A creatinine-height index reflects the body muscle mass and provides important information in sequential studies. A study of blood lymphocytes and of the delayed cutaneous hypersensitivity to common antigens is also helpful because malnutrition may affect adversely the immunocompetence. Rarely more sophisticated studies may be needed to investigate possible malabsorption and specific vitamin, mineral and nutrient deficiencies.

The effort should be directed to prevent malnutrition. However, when there is evidence of malnutrition, one should try to establish the degree and the cause. The cancer, the treatment, and the complications of the disease and the treatment separately or in combinations may contribute to the causation. The malnutrition might also be the result of self-induced changes in the diet in an attempt by the patient to control the cancer and to improve the general health. The patient may omit or decrease the intake of certain foods or may consume large quantities of various nutrients, vitamins and minerals which may cause adverse nutritional effects and toxicities from large quantities of vitamins and certain nutrients.

The disease and the treatment can lead to malnutrition by causing a decreased food ingestion, an impaired digestion and absorption, an external loss of nutrients, and a competition for nutrients between the tumor and the more aggressive partner the host, with the host losing to the tumor. Furthermore by an unknown mechanism the cancer may induce the tumor-free tissues of the host to spend an inappropriately high basal metabolic energy which leads to a state of negative balance of calorie intake and expenditure.

Anorexia as a systemic effect of the cancer itself is the primary reason for a decreased food consumption. The pathogenesis of the anorexia remains speculative and only the control of cancer results in improvement of appetite; there are no drugs that can stimulate appetite in the anorectic cancer patients. Another effect of cancer is the symptom of early satiety or easy feeling the pathogenesis of which again remains unclear in most instances. In addition to these direct effects of cancer on the mechanism of hunger and satiety, there are also indirect causes for a decreased food intake such as psychological and emotional reactions to the disease, pain and insomnia and alterations in the sense of smell and taste that influence acceptance or rejection of foods.

A drop in calorie intake may also be caused by interference with food ingestion if the cancer is strategically located in the oropharyngeal area, the esophagus, or the stomach, or if surgery, radiotherapy or chemotherapy create problems with chewing and swallowing.

Impaired digestion and malabsorption of nutrients may result from a cancer of the stomach, pancreas, or biliary tree, from lymphoma of the small intestine or mesenteric lymph nodes, in the presence of ascites, after a gastrectomy, or resection of part of the small intestine, from intestinal fistulas, and from post-radiotherapy or post-chemotherapy enteritis. Albumin may be lost in the urine in nephrotic syndrome associated with cancer and in the intestine in protein-losing enteropathy. The tumor also as a more aggressive partner may deprive the host of certain vitamins and amino acids and create a relative deficiency for the host.

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The cancer and the complications of the disease and the treatment may raise the basal metabolic energy expenditure to higher levels than before the appearance of the disease and with the same food consumption as before, this may result in a negative calorie balance. The control of the complications and the chemotherapeutic control of the cancer may be followed by a drop of the basal metabolic rate.

In general the caloric needs after the development of the disease are higher than before. With progression of the disease and with various therapies, the needs for specific nutrients, vitamins and minerals may change. However, the nutritional needs in cancer vary so much from person to person and in the same person from time to time during the course of the disease and with different treatments, that it is totally unrealistic to provide a simplified nutritional formula for the total calories and proportion of protein, carbohydrate and fat. Instead, the nutritional program should be totally individualized and periodically re-evaluated and readjusted to meet the patient's specific changing nutritional needs and dietary and eating peculiarities.

Patients who receive radiotherapy or chemotherapy frequently have inadequate or imbalanced dietary intake and develop major nutritional problems. For oral feeding of such patients, the common food blenderized and liquified given in small frequent feedings may provide adequate calorie intake. A regimen of nibbling or rather of widely spaced large meals may be more realistic for these anorectic and nauseated patients. However, their intake should be evaluated frequently and additional efforts made to increase it if it drops.

When problems with mastication and deglutition, or when esophageal or gastric obstruction are present, a nasogastric, esophagogastric, gastric (gastrostomy) or jejunal (jejunostomy) tube should be inserted and for feeding, either the common family food blenderized and liquified or commercial preparations should be used. Because a bolus might cause diarrhea and occasionally manifestations of the dumping syndrome, the feedings should be given slowly. A mechanical pump is more dependable than gravity flow or drip feeding to administer a certain volume per unit time. In patients receiving hyperosmolar and high protein feedings, the water balance should be evaluated and corrected daily. If there is no glucose in the urine a specific gravity higher than 1.020 should alert one to give the patient more water.

Both for oral and tube feeding the commercially available elemental diets are of great help in the nutritional management of the patient with cancer. They can be given either as a sole source of nutritional support or as a nutritional supplement between meals. These defined diets contain mixtures of pure amino acids or protein hydrolysates, simple carbohydrates, small quantities of essential fatty acids, and other triglycerides, minerals and vitamins. They have features that are very helpful in the nutritional support of such patients.

When the elemental diet is given as the sole source of total nutritional support, it is very difficult to voluntarily consume the required volume orally and in such a case a small pliable nasogastric tube should be inserted, to secure total control of the caloric and fluid intake. For supplements between meals a variety of flavors may be kept refrigerated so the patient can have a choice of flavor, however usually a rapid flavor fatigue develops.

Total parenteral alimentation (TPA) plays an important role in the nutritional management of selected patients with advanced cancer. It can provide all the nutritional requirements for prolonged periods during and after the administration of effective chemotherapy which is very toxic to the gastrointestinal tract. This assures better tolerance of antineoplastic therapy and probably better therapeutic results. The patients selected for TPA should have a cancer that is potentially controllable with surgery or radiotherapy and responsive to available chemotherapy. Otherwise there is no indication for TPA in the patient with advanced cancer.

The infusion of concentrated hypertonic nutrient preparations in quantities and composition individualized for the patient requires the insertion of a catheter into a central vein, usually subclavian. However, parenteral alimentation for short periods can be given also in a peripheral vein in the form of a 10% fat emulsion (Intralipid) concomitantly with glucose, free amino acids, electrolytes and vitamins and minerals. Administration of Intralipid and amino acids with sugar should be through a separate IV needle or through the same needle or catheter but with a Y connector at the needle hub or catheter end so the mixture of the fat emulsion with the amino acid solution can take place very close to the vein. This way precipitation of the fat emulsion is avoided.

It is generally accepted that maintenance of a good nutrition during the management of cancer contributes to a better quality of life and probably to a longer life.

References will be found on page 552.

Immunotherapy in Cancer

Current Status and Future Prospects

GERALD VOSIKA, M.D.*

THE CLINICAL role of immunotherapy in human cancer is currently limited to possibly three well defined areas. This includes its use in the treatment of recurrent cutaneous malignant melanoma, and its use as adjuvant therapy in patients with malignant melanoma and lung cancer. These three areas all represent the clinical use of nonspecific immunotherapy.

Active immunotherapy is classically divided into two areas: non-specific and specific immunotherapy. Non-specific immunotherapy refers to the use of agents which increase the overall immunocompetence of the patient. Specific immunotherapy refers to the use of vaccines employing unique tumor associated antigens.

The goal of non-specific immunotherapy is to increase the overall immunocompetence of the host with the expectation that this will increase the host response to its cancer. Agents commonly utilized include biological materials and chemical agents. Although these agents are "non-specific," they may result in tumor destruction by either non-specific mechanisms or by the development of a specific tumor immunity.

Agents that have been used in non-specific immunotherapy include biological agents such as bacillus Calmette Guerin (BCG), the methanol extracted residue of BCG (MER), *Corynebacterium parvum*, thymosin, and cell wall skeleton from mycobacterium as well as chemical agents such as levamisole, cord factor, and dinitrochlorobenzene (DNCB).

Until recently, the field of non-specific experimental and clinical immunotherapy has been dominated by BCG. This material represents a crude, viable and largely immunologically inert (on a weight basis) preparation. In addition, there is an associated morbidity and occasionally mortality with its administration. While many uncontrolled clinical trials with BCG were initially encouraging, these have not been substantiated by well-controlled clinical trials. Although the negative trials are discouraging, these failures can be, in part, due to the route, dose, timing, potency and other factors in the clinical design. Therefore, negative clinical trials, while indicating the ineffectiveness of a given protocol, do not indicate that the approach is invalid. Despite many negative trials, BCG is promising in several areas as noted.

In lung cancer, the initial clinical observation that patients who had empyema post-operatively lived longer and had a lower recurrence rate led to a controlled trial of intrapleural BCG. Data from this randomized trial indicated that in select patients, intrapleural BCG is an effective agent in reducing the recurrence rate. Although the exact mode of action is uncertain, BCG likely activates pulmonary and pleural macrophages which then are capable of "non-specific" recognition and destruction of residual malignant cells. Confirmation of this clinical study is needed.

The second clinical area in which BCG appears promising is more controversial. That area is the use of BCG adjuvant therapy for patients with malignant melanoma with a high risk of recurrence. Despite several negative controlled trials, there are two positive non-controlled trials and two controlled trials in progress which indicate a decrease in recurrence in the BCG treated patients. The final results of these trials will be of interest and may justify increased clinical use of BCG in this area.

A third area of clinical activity for BCG is in the management of recurrent cutaneous malignancy. Several investigators have obtained up to 80% regression of injected cutaneous lesions. In about 20% of cases, non-injected lesions also regress. Occasionally subcutaneous lesions also respond, but consistent results can only be expected in cutaneous disease. Many of these patients with limited regional cutaneous disease will have long term remissions. The use of BCG is therefore justified in these patients prior to chemotherapy.

Corynebacterium parvum has been utilized as an intravenous immunotherapeutic agent in a wide variety of clinical trials. Most trials have employed a two-arm study comparing chemotherapy to chemotherapy plus immunotherapy. The overall results suggest that immunotherapy with C-parvum is helpful in prolonging response rates. MER which is given intradermally has been evaluated in several prospective studies. Most studies have compared chemotherapy plus MER to chemotherapy alone. Results to date indicate no consistent activity. Little clinical data is available on other agents. A recent review of clinical immunotherapy trials was largely negative. Despite the discouraging results to date, there is increased enthusiasm for continued studies. The basis for the enthusiasm is new basic knowledge of the immune system and cancer, and the availability of new purified active immunological agents.

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An active area of basic and clinical investigation is into the specific mechanism of immunosuppression associated with cancer. It is now becoming possible to ascribe clinical immunoincompetence to one of several mechanisms. Some currently described and measurable mechanisms are: soluble tumor produced immune suppressors, suppressor T lymphocytes, prostoglandin producing suppressor cells, suppressor monocytes, and effector cell depletion.

Knowledge of specific mechanisms of immunodeficiency (immunodiagnosis) together with a knowledge of the immunological effects and mechanism of action of immunomodulators is a major goal of current work which will permit a rational approach to immunotherapy. Hopefully, specific drugs can eventually be utilized to correct specific immune defects, thereby restoring reactivity in the immunoincompetent patients. Thereafter, specific drugs to increase general and specific immunoreactivity can be utilized.

The current trend in non-specific immunotherapeutic agents is away from BCG and toward purified non-viable, non-toxic immunologically active components. Recent progress has been made at isolation of the active components of BCG. Studies have indicated that two components, the outer cell wall skeleton and a mycolic acid, when attached to oil droplets and injected intralesionally is as effective as BCG in causing regression and cure of transplanted guinea pig hepatoma. The advantage of these materials is preservation of the biological activity with reduction of the toxicity and the use of a non-viable agent. Clinical trials currently in progress with cell wall skeleton have demonstrated activity in patients with malignant melanoma in initial Phase I-II type studies. The material is currently being used by two institutions (the MD Anderson Hospital and the University of Minnesota).

Other non-specific immunomodulators, high molecular weight polysaccharides (glucans), which are structurally similar to cell wall skeleton, are also being used in experimental models and initial uncontrolled clinical trials with encouraging results.

The mechanism of action of these bacterial agents are probably two-fold. On the one hand, they all activate macrophages. Such macrophages are then able to recognize and destroy tumor cells non-specifically. It is likely that they also increase immunity to specific tumor antigens since ·animals so treated become specifically immune to the tumor. The continued development and clinical use of purified bacterial materials will permit an accurate assessment of their individual clinical activity and mechanism of action not previously possible with crude materials. This basis knowledge can subsequently be used in the design of future therapy trials.

A further exciting development that is currently in progress is the experimental and clinical investigation of the use of endotoxin. Endotoxin has been known for years to cause tumor necrosis. It also causes shock and death which has prevented its clinical application. Recently, a mutant endotoxin has been isolated from certain bacteria which is non-toxic and extremely effective in causing regression of experimental tumors. The mechanism of action is via the macrophage. Endotoxin induces, in a previously activated macrophage, the production of a "tumor necrosis factor." It is this material which is responsible for the tumor destruction. Clinical trials of endotoxin are in their infancy.

In addition to the afore-noted agents, increased interest and study is being given to other defined immunomodulators. This includes levamisole, antihemetic, and purified thymic hormones. Both of these drugs increase T cell activity as measured by lymphocyte surface markers. Both of these drugs are being employed in randomized phase III trials of chemotherapy versus chemotherapy plus immunotherapy.

Finally, it must be noted that immunoenhancement is a real phenomena. Immunotherapy today is an experimental, potentially harmful modality. The use of new potent agents requires careful clinical trials and immune-monitoring of patients such that cause-effect can be clearly discerned. The role of immunotherapy is not established therapy except, perhaps, in the treatment of recurrent cutaneous melanoma, and in the prophylaxis of melanoma and lung cancer.

See reference page 552.

Rheumatology Corner

Malignant Disease and Rheumatism

RICHARD H. FERGUSON, M.D.*

MALIGNANT DISEASES often present with peripheral joint, spine, or muscle symptoms which may provide an early clue to the correct diagnosis. More often, unfortunately, such symptoms serve to obscure the underlying disease and result in a delay in its recognition and appropriate treatment.

Gout

Accelerated nucleic acid production and breakdown by neoplastic tissue often leads to hyperuricemia and hyperuricosuria. This is particularly apt to occur with chronic myelocytic leukemia, lymphoma, multiple myeloma, and occasionally acute leukemia. However, it may complicate any rapidly growing neoplasm, especially when metastatic. Aggressive treatment with radiation and/or chemotherapy may trigger an attack of gout or renal shutdown from urate precipitation in tubules as a result of a sudden surge of uric acid derived from nucleoprotein breakdown. Allopurinol is the agent of choice in preventing renal failure or stone formation in this form of gout.

Pulmonary Hypertrophic Osteoarthropathy

Bronchogenic carcinoma is the leading cause of this syndrome. However, it may result from any intrathoracic malignancy, primary or metastatic, as well as chronic pulmonary sepsis, cyanotic heart disease, inflammatory bowel disease or cirrhosis.

Clubbing of the nails is the hallmark of this entity. It tends to develop rapidly in malignancy and is characterized by periungual reddening, sweating, and increased warmth of the hands and feet, together with non-pitting edema. Bone tenderness is prominent and aching is particularly troublesome when the extremities are dependent. The nails become more convex, both in sagittal and cross section, and the base of the nail may loosen. Joint effusion often occurs, particularly in the ankles or knees, but synovial analysis is nondiagnostic. X-rays of the hands or feet demonstrate a highly characteristic periosteal proliferation over the distal shafts of the long bones. Successful treatment of the tumor results in regression of the musculoskeletal symptoms, and subsequent recrudescence of osteoarthropathy may herald neoplasm recurrence.

Dermatomyositis/Polymyositis

The relationship of inflammatory myopathy to malignant disease remains controversial. Apparently, the past estimates of the frequency with which cancer and inflammatory myopathy coexist have been much too high. Contemporary studies indicate that 8 percent of patients with dermatomyositis/polymyositis have a malignant disease. However, this figure was derived by including cases with cancer preceding the myositis by as long as five years and cases in which the myositis preceded the recognition of malignancy by as much as six years. As would be expected, most patients with cancer are older than 50 and the sex frequency has been equal. Treatment of the malignancy successfully has at times been associated with remission in the myositis or dermatitis, but not invariably. Response to steroid therapy has likewise been variable in this setting.[1] One should remain alert to the possibility that the use of immunosuppressive drugs in the management of refractory polymyositis may result in the development of malignancy later.

Skeletal Metastases

It is recognized that bone lesions may at times simulate disc disease by producing a radiculopathy. The localization of such lesions may mimic monoarticular joint disease or bursitis occasionally. Involvement in the shoulder or hip girdle may lead to confusion with polymyalgia rheumatica. This is particularly true when such systemic features as malaise, weight loss, anemia, and elevated sedimentation rate are associated. The pain of skeletal metastases often has an agonizing, steady, boring quality which may interfere with sleep. Unfortunately, X-rays may not show metastatic changes for several months or the early changes may be too subtle for detection. Sometimes the clinician's first inkling that the diagnosis of polymyalgia rheumatica is erroneous comes with the failure of the patient to respond to steroid therapy in the usual dramatic fashion. Bone scan using technetium polyphosphonate may show metastatic lesions before X-rays are diagnostic. On the other hand, abnormal joint scans of the shoulders using technetium pertechnetate have been found in most patients with polymyalgia rheumatica.[2]

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Leukemia

Acute leukemia in childhood is often confused with rheumatic fever or juvenile rheumatoid arthritis in its early phases. There is often migratory polyarthalgia or polyarthritis along with bone tenderness. Changes occur most often in large peripheral joints but may affect fingers and toes as well. X-rays in the child may show a narrow transverse band of diminished density, paralleling the epiphyseal line. Altered trabecular patterns, cystic areas and demineralization may be found. In the adult with acute leukemia, only 4 percent have predominant osteoarticular symptoms. X-ray changes are uncommon in the adult but hematologic findings usually clarify the picture without delay.

Lymphoma

Hodgkin's disease may involve the spine or other parts of the skeleton. In such instances, pain is the usual presenting feature and often antedates the x-ray change. The appearance of mixed osteolytic and osteosclerotic lesions in the spine combined with anterior erosion of the vertebral bodies is characteristic of Hodgkin's disease. Mediastinal involvement may result in hypertrophic osteoarthropathy.

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Continuing Medical Education

July 21-22, 1979 — University of Minnesota

AMA'S Regional Continuing Medical Education Program, Sheraton-Ritz Hotel, Minneapolis. Sponsor: University of Minnesota Medical School, Minnesota Medical Association, and the American Society for Clinical Pharmacology and Therapeutics.

July 26-29, 1979 — Breezy Point Resort — Brainerd

Symposium on Cardiac Rehabilitation for Physicians & Allied Health Personnel, Breezy Point Resort, Brainerd. Co-sponsors: Divine Redeemer Memorial Hospital, American College of Sports Medicine and Minnesota Medical Association. Ronald Dietzman, M.D./Jose Canto, M.D. 612-450-4552 or 455-1214.

August 22, 1979 — Hennepin County Medical Center

Sleep Disorders in Clinical Medicine, Hennepin County Medical Center, Minneapolis. Sponsor: University of Minnesota 612-373-8012.

September 13, 1979 — Mercy Medical Center

Symposium — Problem Oriented Record Keeping, Mercy Medical Center Auditorium, Coon Rapids. Sponsor: Health Central Inc. (Mercy Medical Center, Unity Hospital, Golden Valley Health Center) Contact: Joseph Cardamore, M.D.

Health Care Cost Commission

The House of Delegates at the May annual meeting thoroughly dissected and acted upon the recommendations of the Cost Commission Report. Their conclusions are now brought to the entire membership. The debate was vigorous; some issues controversial; and the final action encouraging. With few exceptions the recommendations were either fully approved or approved in principle as had been recommended by the Board of Trustees. The delegates soundly rejected attempts to defer action at this time. In this report, they bring to the membership a clearly defined concensus and a commitment to continue our Association's participation in a search for remedial action that addresses cost containment in health care.

Recommendations 1 through 4 and Recommendation 41 are the fundamentals of the report. These recommendations address the creation of an effective pluralistic delivery system, instituting cost sharing as an integral part of this pluralistic system, and finally creating a coalition of forces, charged with the task of facilitating appropriate implementation of the recommendations of the report. With the approval in principle of Recommendation 41, the House of Delegates made the fundamental decision to actively participate in shaping the changes that most certainly are occurring and will continue in the future. They have endorsed a strong voluntary effort by the private sector as an alternative to ever increasing governmental rules and regulations leading to total federal control of the practice of medicine. This effort to preserve freedom in the practice of medicine would have been severely frustrated and crippled had the House of Delegates denied our responsibility and opportunity to participate in this effort. The challenge is now clearly with the leadership and entire membership of our Association

Several of the other 36 supportive recommendations of the report were the source of considerable misunderstanding and controversy. Most notably was Recommendation 8 which addressed the contractural arrangements of the so-called hospital based physicians. Much of the controversy was a product of misinterpretation of intent. The Commission clearly did not intend to recommend fixed salaries for any physician contrary to his free choice. It did, however, feel it appropriate to examine existing contractural arrangements to encourage cost sensitivity. The debates that this recommendation engendered were not without merit. They did give to our membership timely visibility of existing practices and provided a platform for open discussions of some of the interdisciplinary ferment that could threaten the cohesiveness of our membership. Interspecialty differences of many sorts such as inequalities in reimbursement practices will continue to exist. Hopefully these can be resolved internally by intelligent people without splintering the ranks of medicine.

The emphasis that the Cost Commission Report was given by both the Board of Trustees and the House of Delegates should not be translated as a basic alteration in priorities by the leadership of the Association. We are primarily a professional and scientific organization dedicated to the promotion of better health care for the public. We can only accomplish this end by preserving the economic and personal freedoms that have brought us to our present point of academic and professional achievement.

The leadership of the Association has not strayed from its fundamental purposes. It must, however, make value judgments as it allocates its limited resources to accomplish its goals. Therein lies room for differences of opinion.

A recent editorial in MINNESOTA MEDICINE does discredit to the Board of Trustees as it misinterprets well thought out allocation of resources targeted to idealism in goals. Changing times demand flexibility in strategy and resource application. Such does not alter the basic objectives of the Association. It is unrealistic to translate current efforts as a ''Shift in Emphasis'' by the leadership of the Association.

This endorsement of the intent of the Cost Commission Report by the House of Delegates is a directive to the Board to continue to expand its efforts in the political and socio-economic arenas, so that we as an association of professionals exert every effort to preserve our freedoms and promote scientific excellence.

Richard J. Frey, M.D.
Chairman
Health Care Cost Commission

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Index to Advertisers

Anderson, C. F. Co. 502

Army Reserve 554

Beltone Electronics Corp. 518

Bream Gallery 474

Burroughs-Wellcome Co. 510

Classified Advertising 561

Hearing Instrument Dispensers Guild 478

Lilly, Eli & Co. 476

Mead Johnson Pharmaceutical Division 483, 484, 485, 486

Medical Protective Company 526

Merrell-National, Inc. 502, 503

Merck Sharp Dohme 474

Minnesota Medical Association 560

Roche Laboratories .... Cover 2, 506, Cover 3, 4

Smith, Kline & French 505

United States Air Force 526

Upjohn Company 504

Physicians Act on Cost Commission Report

Here is an item-by-item summary of the Minnesota Medical Association House of Delegates action on the 41 recommendations in the Report of the Commission on Health Care Costs 1979.

1. **Organize New Health Care Plans**

   Employers, insurers, providers, and interested community leaders should support the development of new and existing health care plans by providing managerial and marketing expertise — and financial support, if necessary — to providers who are forming new plans.

   Providers should review both the existing health care plans and proposed health care plans to identify those plans that may be consistent with their own style of practice. The Commission urges physicians to seriously consider participating in such plans.

House of Delegates: Approval in Principle

2. **Promote Market Forces**

   Employers offering health benefits should create a fair market for health care plans by offering their employees multiple choices among conventional insurance plans and alternative health care plans. In order to insure that fair market conditions prevail among these choices, the following conditions must be met:

   - the employer should contribute the same amount of money toward the premium of every choice available
   - the difference between that amount and the chosen plan's actual premium should be paid by the employee or returned to him or her in another benefit form depending on whether the premium is more or less than the employer's contribution

   Unions should negotiate for multiple choice in their contracts to insure that each employee has individual choice of the plan best suited to his or her needs.

   Employers and unions should actively promote the concept of choice to employees and provide simple, comparative information about all available choices.

   The market and the opportunity to make fair market choices should be expanded quickly to all consumers including, but not restricted to, the groups below:

   - Medicare/Medicaid recipients
   - employees whose employers offer low benefit packages or do not offer health care benefits
   - the self-employed
   - part-time employees
   - government employees

House of Delegates: Full Approval

3. **Eliminate Barriers to a Competitive Marketplace**

   Competitive bidding among hospitals should be encouraged, provided that:

   - the competition is subject to the same rules as are other competitive industries and as permitted under the laws of Minnesota
   - private paying patients are not subsidizing groups

   Health care plans should have the latitude to design whatever set of benefits and premium charges they deem most marketable in a given employee population.

   Legislation and regulation that limit the flexibility of the individual delivery system should be discouraged, and existing laws and regulations that have this effect should be repealed or amended. Recognizing legitimate differences between health care plans and insurance plans, the Commission believes that laws should have an equivalent effect on the marketing of each.

House of Delegates: Approval in Principle

4. **Institute Cost-Sharing**

   All insurance plans or health care plans offered within the state should have cost-sharing provisions specifically directed toward discouraging immoderate or indiscriminate use of services. Cost-sharing should not, however, be a barrier to necessary therapeutic and preventive care. In addition, any secondary coverage eliminating appropriate cost-sharing should be discouraged within the state. Lastly, employees should be offered a choice of plans that utilize different amounts of cost-sharing and those differences should be reflected in the plans' respective premiums.

House of Delegates: Full Approval

5. **Utilization Review**

   Major employers in the state should exert pressure on major insurers to take steps to reduce inappropriate utilization.

House of Delegates: Approval in Principle

6. **Second Surgical Opinion**

   The Minnesota Medical Association should evaluate the studies done on second surgical opinion programs and monitor the results of the pilot testing presently being conducted within the state and elsewhere.

   Should the data indicate that either substantial cost-savings or improvement in the quality of care are possible, the Medical Association should make strong recommendations to employers and insurers that this program be adopted — possibly on a mandatory basis — throughout the state. Should the program be determined to be without merit either in terms of cost or quality, then the program should be disbanded.

House of Delegates: Full Approval

7. **Feedback for Physicians**

   The Foundation for Health Care Evaluation should include in the patterns of practice that are presently being generated criteria for cost-effectiveness as well as for quality. In addition, each practicing physician should be supplied with distributions of aggregate data and his or her own personal profile to compare with these distributions.

House of Delegates: Approval in Principle

8. **Hospital-Based Physician Compensation**

Hospitals and their medical staffs should re-examine their compensation arrangements with contracted hospital-based physicians and devise compensation systems that encourage cost-sensitivity. Placing these contracted physicians on a fixed salary may be the first step in this direction.

House of Delegates: Not Support and Instead Endorse Report R of the AMA Board, Adopted by the AMA House in June, 1977. (Report R available at MMA)

9. **Health Promotion by Physicians**

Analysis of risk factors and lifestyle characteristics should be included in the routine physical exams given by every primary provider in the State of Minnesota. This analysis should include such determinations as:

- smoking habits
- physical activity level
- nutritional patterns
- chemical usage (alcohol, drugs, caffeine, etc.)
- weight, blood pressure, cholesterol levels, etc.

Should a patient be determined to have risk factors, the physician should advise the patient to work on reduction of the risk factors and refer him or her to behavioral counselors within the physician's clinic or outside agencies specializing in such interventions.

House of Delegates: Approval in Principle

10. **Health Promotion by Industry**

Major industry should actively experiment with health promotion programs in order to counteract the problems of absenteeism, excess numbers of sick days, and rising health insurance premiums. Some methods that should be considered are:

- development of in-house health promotion programs
- selection of reputable programs in the community and sharing of the fees for such programs with employees, providing that their attendance is good and that objective changes in risk factors last over sufficiently long periods to demonstrate that the changes are not temporary
- careful evaluation of the impact of these programs on morbidity, disability, absenteeism, productivity, etc.
- encouraging employees by means of incentives (for example, bonuses, earned days off) to participate in programs or "healthful" behavior patterns that demonstrate cost-effectiveness

House of Delegates: Approval in Principle

11. **Health Promotion by Third Party Payers**

Health insurance carriers should conduct pilot studies on tying premium charges to risk factors and lifestyle characteristics such as smoking patterns and level of physical activity. Particular attention should be paid to those risk factors under the control of the individual. Furthermore, third party payers should review intervention programs and identify their cost effectiveness. Should the programs be determined to be cost effective, third party payers should consider extending coverage to them.

House of Delegates: Full Approval

12. **Length of Stay**

Hospitals should perform concurrent utilization review and quality assurance review (retrospective quality audits) for a sample of patients regardless of payment source.

During concurrent review, should the care already rendered be found to be obviously inappropriate, the hospital and the attending physician should be at risk. If the provider indicates to the patient that additional hospital care is not medically indicated, the patient should be advised that any additional hospital care will have to be paid for at his or her expense. Should retrospective review reveal a repeated pattern of overutilization, a program of sanctions should be implemented in the institution involved.

House of Delegates: Refer to Board for Further Study and Return to House for Final Action

13. **Treatment Modalities**

The medical specialty societies in Minnesota should define acceptable treatment modalities and conduct controlled studies with clearly defined protocols to determine the costs and benefits of these various modalities, including the alternative of no treatment whatsoever. Such factors as quality of life and improvement in productivity should be measured along with morbidity and cost in the studies.

Reimbursement for existing treatment modalities should continue only if the professionals involved are willing to participate in such studies. Furthermore, all new treatment modalities should go through such an evaluation process prior to reimbursement by third party payers, and no new clinical treatment should be approved for reimbursement without its cost-effectiveness demonstrated. In cases of dispute regarding reimbursement, the third party payers could turn to the specialty societies for judgment.

House of Delegates: Approval in Principle

14. **Clinical Practices**

Agencies and federal, state, and private foundations which fund studies of clinical practices should require cost-benefit analysis and rigorous outcome evaluations in grant work.

House of Delegates: Approval in Principle

15. **Graduated Levels of Care**

Third party payers should promote development of adequate insurance coverage for high quality care rendered in the most cost-effective setting. Among the types of services to which coverage should be extended — provided that they are demonstrated to produce a net reduction in services rendered, thus reducing the cost of health care to the community as a whole — are:

- health services delivered out of a hospital setting
- skilled intermediate services and facilities
- home health care
- ambulatory care
- hospices
- community services provided by hospitals

House of Delegates: Full Approval

16. **Preadmission Testing**

Third party payers should encourage preadmission testing on an out-patient basis in order to reduce hospital utilization. These tests should be of high quality and performed in the most appropriate setting. Reimbursement should be made on the most favorable basis under the contract, which may mean modifying or waiving both the deductible and the coinsurance clause.

House of Delegates: Reaffirm Existing Policy

17. **Emergency Room Utilization**

Physicians should explore ways to reduce emergency room usage by their patients by considering such policies as:

- ''lunch hour'' coverage in physicians' offices to avoid unreferred emergency room visits
- shared telephone screening systems with other physicians within a practice or with other practices in the area
- lengthened office hours on a rotating basis in either physicians' offices or clinics and, if necessary, appropriate arrangements with other offices that are geographically proximate, to lengthen the ''business day''

Third party payers should penalize indiscriminate use of the emergency room by:

- adding appropriate copayments or deductibles to emergency room use
- eliminating favorable treatment (reimbursement) of procedures done in the emergency room instead of in a physician's office

Physicians in the emergency room should:

- conduct no investigative work without first contacting the patient's physician, except in cases of real emergency
- advise the patient to get a primary care physician if he or she does not have one

Consumers should be furnished with a self-diagnostic handbook that advises them when to call a physician and what to tell him or her, and when to go to the emergency room.

Last, a public campaign should be undertaken to inform consumers of the excessive costs of emergency room use and of the benefits both in cost and in quality of care attainable through having a primary provider.

House of Delegates: Approval in Principle

18. **Emergency Room Practices**

Every hospital having an emergency room should review both its staffing patterns and its modes of practice, and institute whatever changes may be indicated to increase cost-effectiveness.

House of Delegates: Full Approval

19. **Hospital Capacity Reductions**

Recommended reductions in hospital capacity in a community should be based on a generally accepted policy framework; careful measurement of community needs; a cost-effective priority system; a plan for resolving such issues as resulting unemployment, debt payment, and retention of health care professionals within the community; and, finally, a proposal that has been agreed upon by key parties in the community health care system for an orderly process of carrying out the overall strategy.

House of Delegates: Approval in Principle

20. **Reducing Capacity in Rural Areas**

A study focusing on the hospitals outside the seven county metropolitan area should be undertaken by the State Health Planning and Development Agency. This study should evaluate the social, economic, professional, and legal implications of:

- closing entire hospitals
- sharing services between hospitals
- closing services within a single hospital

House of Delegates: Approval in Principle

21. **Financial Compensation for Closure**

If publicly mandated closure forces a hospital to close on the basis of excess capacity alone and it is demonstrated that the bondholders or other creditors will suffer economic loss despite sale of land or building, then public funds should be made available from the state and/or federal government to provide relief.

House of Delegates: Full Approval

22. **Revising Hospital Rate Structures**

The hospital rate structure for acute-care services should be modified so that revenue produced by specific services covers the cost of providing those services, thereby preventing — insofar as possible — the subsidizing of services not producing enough revenue to meet their costs.

House of Delegates: Approval in Principle

23. **Medicare/Medicaid Reimbursement**

Medicare and Medicaid should reimburse institutions on a basis that discourages subsidy by private-paying patients.

House of Delegates: Full Approval

24. **An Information Clearinghouse**

An information clearinghouse should be established that identifies and locates literature on the latest strategies and techniques in the area of hospital administration, and literature reviews on selected subjects should be available upon request.

Hospitals should use these services and adopt promising techniques as they are identified.

House of Delegates: Full Approval

25. **Hospital Boards**

Members of the Board of Directors of hospitals should become even more active in promoting strategies for cost containment in the hospitals. They should make increasing demands on administrators for well thought out plans for cost analyses, efficient staff allocations, and means of reducing capacity such as merging, consolidations, and sharing services with other hospitals.

House of Delegates: Full Approval

26. **Desirable Practice Patterns**

Criteria for desirable patterns of cost-effective practice should be developed for broad disease categories. Once developed, the criteria should be published in the professional journals to increase their dissemination and utilization.

27. **Medical School Curricula**

Once the criteria for desirable practice patterns for various disease categories are developed, they should be incorporated in the proper courses in medical school curricula. Criteria should be developed first for inclusion in the basic clinical courses required of most medical students.

28. **Clinical Reviews and Case Presentations**

As the criteria for cost-effective patterns of practice are developed, they should be incorporated in clinical reviews. Evaluation of case presentations should include consideration of these criteria as well, and they should take their place alongside clinical indications in discussions of adequacy of care rendered.

30. **Continuing Medical Education**

As the criteria for cost-effective patterns of practice are established they should become an integral and substantial part of Continuing Medical Education programs. In specific Continuing Medical Education courses, physicians should be required to consider the costs implicit in the procedures under discussion.

31. **Cost-Effectiveness in Audits**

As the criteria for cost-effective patterns of practice are developed, they should be included routinely in audits of medical quality.

Recommendations 26, 27, 28, 30 and 31 Were Approved in Principle Based on the Following Restrictions:

1) Physicians must be involved in determining the conceptual and operational definitions of "criteria"
2) Physicians must be involved in determining the "criteria" themselves and how they will be used.
3) The "criteria" must continually be re-evaluated (as new information becomes available) and modified.
4) Use of the "criteria" must be in a program which is educational in its intent and practice. Additionally, the program must be designed to minimize the use of "criteria" as a punitive tool.
5) The "criteria" must be sensitive to local situations and must be adaptable to local needs and reflect appropriate local practice patterns. Regional, state and national guide lines if developed, must be developed in such a way as to encourage local modification.
6) The cost of the development of the "criteria" must be assessed.

29. **Board Examinations**

Where testing for cost-sensitivity is not already included in the clinical management portion of board examinations, the specialty boards of the Liaison Committee of Graduate Medical Education who accredit residency programs should develop such testing mechanisms. Furthermore, inefficient and redundant choices of procedures should be heavily penalized in the scoring of such exams.

House of Delegates: Refer to Board for Further Study

32. **Laboratory and Radiology Use**

A guide should be developed to aid physicians in making cost-effective choices regarding laboratory procedures in the context of an entire episode of care. This guide should contain information about the specificity, sensitivity, approximate price, and any other useful information that might aid the physician in deciding whether to use a procedure or which of two or more procedures to use.

A similar guide containing analogous information should be developed for radiology procedures.

House of Delegates: Full Approval

33. **Cost-Sensitizing**

Hospital administrators and their medical personnel should devise plans to sensitize their staffs to the costs of procedures typically performed in each department. This "sensitizing" process should occur frequently enough so that physicians and other staff are kept current on costs.

House of Delegates: Approval in Principle

34. **Health Promotion Task Force**

The Health Care Coalition* should establish a *temporary* Health Promotion Task Force charged with two main responsibilities:

- to identify how a health promotion strategy may best be developed and implemented through the state
- to evaluate the cost-effectiveness of intervention programs that already exist and design an evaluation system to uniformly monitor the cost-effectiveness of new intervention programs across the state.

House of Delegates: Approval in Principle

35. **Health Status in School-Age Children**

Minimum standards relating to such areas as obesity, physical fitness, and chemical use should be developed for judging the health and fitness of the school-age population. Where established standards are not met, school districts should focus their curriculum development and intervention efforts in problem areas and be held accountable for meeting these standards.

House of Delegates: Approval in Principle

36. **Obtaining Primary Providers**

Directories of physicians should be published by county that identify specialty, location, characteristics of practice, hospital affiliations, and sample ranges of charges. Also included in this directory should be:

- a glossary of the various specialties and subspecialties
- a decision making guide to assist the consumer in clarifying his or her needs and to familiarize him or her with questions that should be asked of any provider
- a selection process model to guide a consumer in choosing a physician

House of Delegates: Refer to Board for Reconsideration of Existing Policy

37. **Self-Care for Consumers**

Physicians should supply their patients with self-care handbooks and strongly encourage patients to refer to these before making an appointment or going to the emergency room.

Since employers have a vested interest in seeing inappropriate utilization reduced, employers should also supply self-care handbooks and encourage employees to refer to them.

Studies should be conducted to determine whether consumers who use a good self-care guide and are trained in simple data gathering and reporting techniques actually use health care services more appropriately, have higher-quality interactions with health care professionals, and experience comparable or reduced morbidity.

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*See Recommendation 41

House of Delegates: Approval in Principle

38. **Government Regulation**

Any legislation mandating health care benefits or regulation regarding health care must include the provisions below in order to be adopted by either state or federal government:

- a statement of economic impact and some estimate of the benefits to be gained, and a determination of whether such benefits are priced beyond the reach of any segment of the population
- public hearings at which both the legislation or regulation and the statement of economic impact can be subjected to public scrutiny and discussion of the benefits and costs
- a time limit, such as five years, after which a regulation becomes null and void unless a review process, which includes public hearings, reaffirms the need for such regulation.

All public and private health care institutions, including state and federal, should be subject to the same regulations — such as quality assurance and utilization review requirements — as are other health care institutions.

Finally, the review process above should be extended to existing legislation and regulations and a statement of the costs and benefits of each piece of legislation or regulation should be prepared by the administering agency.

House of Delegates: Full Approval

39. **Certificate of Need**

Certificate of Need, if it proves to be an effective cost-control mechanism, should apply equally to all providers, including state and federal health care institutions, physicians' offices, and clinics.

House of Delegates: Reaffirm Existing MMA Policy Which is Opposed to Extending Certificate of Need to Physicians' Offices

40. **Allied Health Providers**

Ideally, allied health providers should not be used unless it is demonstrated that their involvement is cost-effective or remedies a maldistribution in services.

Allied health providers should not be reimbursed directly unless they are under the supervision or authorization of a physician.

Licensing of allied health providers should occur only when it is absolutely clear that public safety depends on it. Even then the issue of licensing should be recognized as mainly an economic one.

No legislation should be passed that inhibits a physician's use of allied health providers.

Physicians should consider new ways to use allied health providers to deliver high quality care in more efficient ways.

Careful study should be made of the supply of and demand for allied health providers, and state funding should not be made available to training programs unless the demand for the graduates is clearly demonstrated.

House of Delegates: Full Approval

41. **Health Care Coalition**

A nonprofit, tax-exempt Coalition should be established to implement the recommendations of the Commission on Health Care Costs and to monitor health care costs trends in Minnesota so that additional actions may be taken where appropriate.

- The Coalition should be created by the Commission through a special implementing body of three members including the current Commission Chairman. This implementing committee of the Commission on Health Care Costs should be responsible for naming individuals to serve on the Coalition Board of Directors, establishing the number of directors to be appointed, developing guidelines for Coalition activity, approving the first budget in conjunction with the Coalition Board, and arranging for outside financing for the first year. The implementing committee should complete its work following the first meeting of the Coalition Board of Directors.

The budget for the first year should be raised primarily from sources outside the medical profession, and the initial staff should consist of — at least — an Executive Director and one secretary.

The Coalition should prepare an annual report to be submitted to the full Commission on Health Care Costs. The latter group should be reconvened in a year to hear this report.

House of Delegates: Approval in Principle

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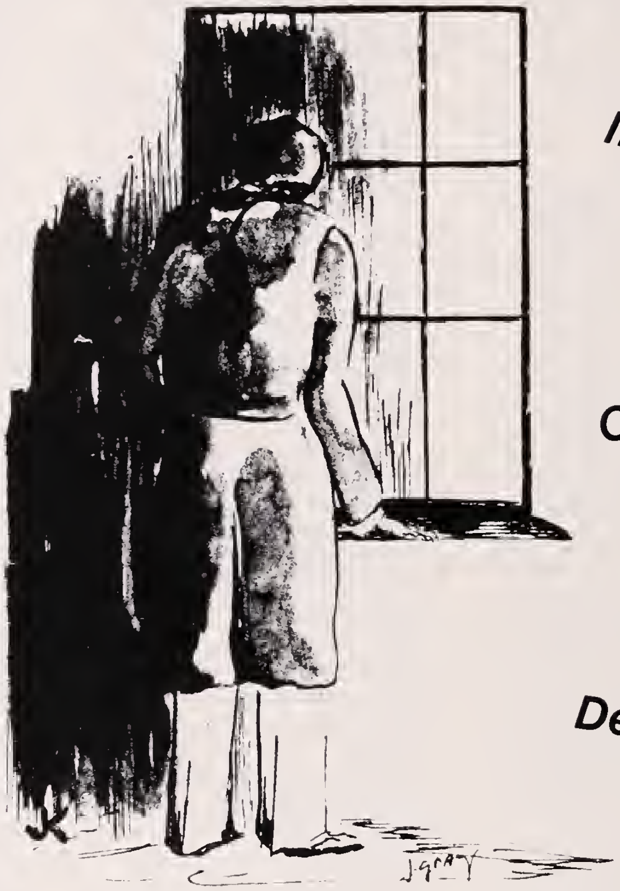
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FAMILY PRACTICE opportunities in outstanding Southern Minnesota Group. The Albert Lea Clinic, P. A., is interested in contacting physician candidates for city and small town branch practices. This group is a 16 man multispecialty group in the primary and secondary care fields. Top salary first year. Senior physician participation beginning at the end of the first year, in incentive income distribution plan. Low cost buy in. Maximum profit sharing plan. Top level insurance plan and full range of other benefits. New hospital in city. Albert Lea is an exceptional place to live and these are choice practices. Please contact B. J. Boss, Administrator, Albert Lea Clinic, P. A., 1602 Fountain St., Albert Lea, MN 56007, Phone 507-373 8251, personal phone 507-377 1406 or contact Gary Boeke, M.D., 507-373 8251, personal phone 507-826-3288.

FAMILY PRACTICE and CARDIOLOGY specialty positions available wtih Mankato Clinic, Ltd. Our 30 man multi-specialty group attracts specialty referrals from a southern Minnesota area of 200,000 population. Excellent group practice opportunity in All-American community with full hospital services; full range of group fringe benefits; liberal time off; salary first year; incentive pay thereafter. For more information call collect R. F. Roskens, Administrator, or Dr. B. C. McGregor, 507-625-1811.

WANTED: GP to join two GP's in practice in rural community northern Minn. Mod. clinic bldg. with good xray & lab facilities. 40 bed hosp; 100 bed nursing home. Also need locum tenans for summer vacations. Contact W. A. Pinsonneault, MD, Warren Clinic, box 107, Warren, MN 56762 (218) 745-4151.

PHYSICIANS—Immediate openings for family physicians, internists at Fergus Falls, Moose Lake, St. Peter and Willmar State Hospitals, Salary $40,000-50,000. Regular hours. Liberal benefits. Call Ronald C. Young, M.D., Dept. of Public Welfare (612/296-3058).

THE FARIBAULT CLINIC, LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

PRACTICE WHERE there is an abundance of clean air and outdoor activities — in the heart of Minnesota's lakes and woods. Excellent opportunity for 1 F.P. to join with 6 F.P's., 2 General Surgeons and 2 Physician Assistants. New clinic building. 50 bed hospital with 5 bed ICU-CCU. Contact William Pauley, Park Rapids-Walker Clinics, LTD., 120 N. Main, Park Rapids, MN 56470. Phone 218/732-3325.

OPHTHALMOLOGIST WANTED IN SOUTHERN MINNESOTA Group Practice. The Albert Lea Clinic, P.A., in Albert Lea, Minnesota, a 16 man multi-specialty group is seeking a replacement for a senior man. Board certified or Board eligible. Salary guaranteed first year. Second year, participant in clinic's incentive income distribution plan. Low cost buy-in arrangement. Profit sharing plan. Top insurance plan with full range of other benefits. New hospital in city. A choice practice and exceptional place to live. Contact William Brouwer, Assistant Administrator, Albert Lea Clinic, P.A., 1602 Fountain Street, Albert Lea, Minnesota 56007, phone 507-373-8251, personal phone 507-889-6381 or contact Gary A. Boeke, M.D., 507-373-8251, personal phone 507-826-3288.

MINNEAPOLIS GROUP practice opportunities in:

Orthpedic Surgery
Child Psychiatry
Adult Psychiatry
Obstetrics-Gynecology
Allergy
Otolaryngology

Group Health Plan is a 20 year old multispecialty group with seven clinics in the Minneapolis-St. Paul metropolitan area. We offer competitive earnings, comprehensive fringe benefits and excellent facilities in one of America's leading metropolitan areas. Curriculum vitae and references invited: John W. Harkness, M.D., 2500 Como Avenue, St. Paul, Minnesota 55108.

(Continued from Page 562)

(Continued from page 561)

DO YOU WANT to own the most beautiful homestead in the Twin City area? For sale by owner (almost new) beautiful spacious 7,200 sq. foot mansion in rural Marine-on-St. Croix on 55 acres, including a beautiful private lake (stocked with fish), with all modern conveniences and 5 fireplaces, 6 baths, 2 swimming pools, 2 large barns and many, many extras. $550,000 — will take Contract for Deed with $100,000 down. 772-1316, 433-3598.

MEDICAL BUILDINGS: We offer specialized Planning, Financing, and Construction services for group practice facilities and medical office buildings. Contact James Verhey, NORMANDALE ASSOCIATES, INC. 4813 Hibiscus Ave. Minnneapolis, Minnesota, 55435. (612) 925-3101.

ENT and OPHTHALMOLOGY specialty positions available with Mankato Clinic, Ltd. Our 30 man multi-specialty group attracts specialty referrals from a southern Minnesota area of 200,000 population. Excellent group practice opportunity in All-American community with full hospital services; full range of group fringe benefits; liberal time off; salary first year; incentive pay thereafter. For more information call collect R. F. Roskens, Administrator, or Dr. B. C. McGregor, 507-625-1811.

FAMILY PHYSICIAN wanted to join active practice with two family physicians and general surgeon. Generous starting salary with a full range of benefits. Located one hour southwest from Twin Cities. Growing community with excellent recreational and educational opportunities. New clinic with community hospital nearby. Contact: Jo E. Anderson, M.D. or Duane R. Schultz, Business Manager, Minnesota Valley Medical Associates, 301 Valleygreen Square, Le Sueur, Minnesota 56058. Phone (612) 665-3391.

WANTED— M.D. or D.O./FAMILY PRACTICE to join gr. of 3 FP/MD's. Exc. new clinic attached to 120 bed hosp. Full hosp. priv. avail. Salary 1st yr. then may join corp. Thriving comm. of 10,000 + with lg. drawing area. Fine recreational and social area with first class school system & all churches avail. Easy freeway access to metro area. Contact Family Clinic, 808 3rd St. S.E., Little Falls, MN 56345 or call collect D. R. Seifert M.D. (days) 1-612-632-2301, (evenings) 1-612-632-9150.

PEDIATRICIAN: Board certified/eligible Pediatrician to associate with an established pediatrician to replace partner who is leaving. Newly remodeled downtown Minneapolis office. Guaranteed salary and/or share in corporation. Contact: Dr. Nancy Lund, 825 S. 8th Street #216 Minneapolis, MN 55404 (612) 336-3369

OBSTETRICIAN-GYNECOLOGIST, to join 11 member primary care group. 7 Family Physicians, 2 Internists and 2 General Surgeons. Large patient population, newly remodeled and expanded Clinic facility approximately 6 blocks from modern, well equipped 99 bed hospital. Rural community 45 minutes South of the Metro area on 35W. Salary guarantee first year. For more information please contact: Darral Mischke, Clinic Administrator, Faribault Clinic, Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

15 DOCTOR MULTISPECIALTY group is looking to add two doctors in the Family Practice Dept.; one doctor in orthopedic surgery, internal medicine and OB/GYN. Recreational, educational and cultural opportunities abound in small town atmosphere of northern Minnesota. New clinic and hospital under construction. Contact D. E. Carlson, Bemidji Clinic, Bemidji, MN 218-751-1280

FAMILY PRACTICE OPPORTUNITIES: Large multispecialty group with active clinic and hospital practice offers opportunities for full range of family practice in suburban setting with one other family practitioner or position in multispecialty clinic setting with limited Ob/Gyn and Pediatrics. Comprehensive fringe benefits and competitive salary. Contact: John W. Harkness, M.D., Group Health Plan, 2500 Como Avenue, St. Paul, Minnesota 55108.

ORTHOPAEDIC SURGEON, Internist and Family Practice for multi-specialty group with a Family Practice Department, Crookston, Minnesota. Located in heart of the Red River Valley, stable economy, good income, new clinic facility, full partner in one year. Call R. F. Schnabel, M.D., 218-281-3184, Crookston, Minnesota.

INTERNIST AND FAMILY PHYSICIANS wanted by 10 person medical group in Alexandria, Minnesota. Please contact Paul H. Engebretson, M.D., 610 Fillmore, Alexandria, MN 56308. Telephone: (AC612) 763-5123"

INTERNIST AND FAMILY Practitioner wanted for congenial democratic seven man group; one General Surgeon, one OB/GYN and five Family Practitioners. Salary in the $40,000 to $50,000 range depending on qualifications; full buy-in privileges and equal partnership after one year of practice. For more information contact JM Doty, MD, FACOG, Medical Center, Little Falls, Mn. 1-612-632-6611.

GENERAL SURGEON or internist needed to take over 27 year practice by May-July, 1980, in two college city. 42 miles from Twin Cities. Write: MINNESOTA MEDICINE — 543 — 101 E. 5th St. #900, St. Paul 55101.

MEDICAL DIRECTOR EMERGENCY/OUTPATIENT Excellent opportunity for board certified physician (internal medicine, emergency medicine, or family practice) to direct the medical component in the all new emergency/outpatient department of our 838 bed teaching hospital. Our emergency room has a primary emphasis, on a regional basis, in cardiovascular. Last year we experienced approximately 30,000 visits. Position involves providing direct patient care, and also quality assurance, audits, JCAH, and coordination of 16 emergency room physicians. For more information regarding benefits, compensation, and accountabilities, contact Clarence Harris, Director of Human Resources (612) 874-5115. Abbott-Northwestern Hospital, Inc., Chicago Ave. at 27th St., Minneapolis, MN 55407. An equal opportunity employer.

INTERNIST: Certified or Board Eligible to join the staff of this 409 bed, University affiliated VA Medical Center located in the Black Hills of South Dakota. Position offers both clinical and academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. This area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD 57741. Phone 347-2511, Ext. 497. Equal Opportunity Employer.

MEDICAL OFFICE EQUIPMENT and furniture: examining table, mercury monometers, splendid office desk, Norelco transcriber. EKG, chairs, etc. Call J. Stevenson, M.D. home phone 724-1198. Reasonable price.

PSYCHIATRIST — Board Eligible or Certified to take charge of a 30-bed ward in this 409 bed, University affiliated VA Medical Center located in the Black Hills. Position offers clinical, and possible academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. Area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD. 57741. Phone (605) 347-2511, Ext. 497. Equal Opportunity Employer.

BEAUTIFUL MEDICAL Clinic with room to expand in Hastings, Minnesota. Excellent investment, located on main highway. Dr's available to leaseback. 20 examining rooms, 3 doctor's offices, 1 large Doctor's lounge, 3 nurses rooms. Over 10,000 sq feet. Asking $450,000. Schumacher-Keller Inc., Realtors, 1545 Vermillion St., Hastings, Minnesota 55033. 1-612-437-3144.

PHYSICIAN'S ASSISTANT — Certified seeks permanent position in Family Practice and/or Surgery. Six years experience Family Practice/Surgery. Previous training and experience in Surgery, Urology, Orthopedics, Ophthalmology, and Dermatology. National Certification by N.C.C.P.A. Previous Minnesota resident and ex-Army Corpsman. Larry Kelso P.A.-C., 406 S.W. 8th St., Aledo, Illinois, 61231.

EXPERIENCED GENERAL SURGEON needed to join two general internists, a gastroenterologist, four family practitioners and a pediatrician in a busy Satellite of the Marshfield Clinic at Ladysmith, Wisconsin. Complete details and personnel interview will be arranged for qualified applicants. Send curriculum vitae, bibliography and three references to William M. Toyama, M.D., Department of Surgery, Marshfield Clinic, 1000 N. Oak Avenue, Marshfield, Wisconsin 54449.

APPLICATIONS WELCOMED from board-qualified or certified radiologists. Large teaching hospital, upper midwest; University affiliation. Subspecialty training in nuclear medicine desirable. Box 529, Minnesota Medicine, 101 E. 5th St., St. Paul 55101.

(Continued to page 564)

(Continued from page 563)

Board certified or eligible general surgeon to join 5 physician family practice group in rural Minnesota: clinic attached to 56 bed acute care JCAH General Hospital serves a population of 25,000: it is 150 miles from Mpls.-St. Paul and 100 miles from Fargo: heart of lakes recreation area: good schools, good housing, etc. Contact D. E. Ness, M.D., V.P. Board of Directors of John S. Studsrud, Administrator, Tri-County Hospital, 418 North Jefferson, Wadena, MN 56482. Send CV with inquiry.

Internal medicine resident to work in 130 bed hospital. Rotating shifts. Starting salary of $22,000/year. Curriculum VITAE to Chief of Staff or Associate Administrator. Divine Redeemer Memorial Hospital, 724 19th Avenue North, South St. Paul, MN 55075.

Board certified or eligible family practitioner to join 5 physician family practice group in rural Minnesota: clinic attached to 56 bed acute care JCAH General Hospital services a population of 25,000: it is 150 miles from Mpls.-St. Paul and 100 miles from Fargo: heart of lakes recreation area: good schools, good housing, etc. Contact D. E. Ness, M.D., V.P. Board of Directors or John S. Studsrud, Administrator, Tri-County Hospital, 418 North Jefferson, Wadena, MN. 56482. Send CV with inquiry.

Associate medical director — A progressive Twin Cities based insurance leader has an excellent opportunity for an individual with experience in general or internal medicine. Minnesota state license required. This position provides an excellent environment for professional development. Competitive fringe benefits include regular working hours, continuing medical education, study time, expenses and professional insurance. Specific accountabilities will be developed based on individual's background and professional interests. Send resume, inquiries and curriculum vita to: Warren L. Kleinsasser, MD, Second Vice President and Chief Medical Director, The Minnesota Mutual Life Insutance Company, 345 Cedar Street, St. Paul, Minnesota 55101, An Equal Opportunity Employer.

Fifty physician multi-specialty clinic in western Wisconsin wants Family Practitioner to work in nearby satellite offices. Excellent cultural, educational and recreational facilities. 90 miles from Minneapolis. Please contact G. E. Owen, M.D., Midelfort Clinic, Ltd., 733 W. Clairemont Avenue, Eau Claire, WI 54701 or call 839-5222.

Knoxville — psychiatrist — excellent professional opportunity, large Neuropsychiatric hospital, immediate vacancies for Board Certified/Eligible Psychiatrist. Strong support staff and facilities. Enjoy benefits of 30 days paid vacation, 15 days paid sick leave (accumulating) per annum; liberal retirement plan; health and life insurance; malpractice shelter; moving expenses paid; HIGHLY COMPETITIVE SALARY to $50,000 with qualifications, license in any state. Contact: Chief of Psychiatry, VA Medical Center, Knoxville, Iowa 50138 Phone: (515) 842-3101, extension 216. EDE

Family practitioner, ob-gyn, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

ROCHE

For recurrent attacks of urinary tract infection in women

Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days

- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice
- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Please see back cover.

Her next attack of cystitis may require

the Bactrim™ 3-system counterattac

19 So. 22nd St.
Philadelphia, PA 19103

ROCHE

Bactrim has shown high clinical effectiveness in recurrent cystitis as a result of its wide spectrum and distinctive antimicrobial action in the urinary, vaginal and lower intestinal tracts.

The probability of recurrent urinary tract infection appears to be enhanced by the establishment of large numbers of *E. coli* or other urinary pathogens on the vaginal introitus. The trimethoprim component of Bactrim diffuses into vaginal fluid in effective concentrations, thus combating migration of pathogens into the urethra.

Studies have shown that Bactrim acts against *Ente bacteriaceae* in the bowel without the emergence of r tant organisms. Thus, Bactrim reduces the risk of intr colonization by fecal uropathogens. It has *no* significant effect on other normal, necessary intestinal flor

Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal trac

Please see reverse side for summary of product information.

MINNESOTA MEDICAL ASSN.

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"St. Paul Skyline" E. Theodore Palm, M.D.

August, 1979

vol. 62 #8

25 Years of Psychopharmacology
Special Issue
Part II

A character all its own.

ROCHE 5 VALIUM
ROCHE 10 VALIUM

Valium (diazepam/Roche) is a benzodiazepine with a character all its own. Pharmacologically, it is a potent skeletal muscle relaxant and anticonvulsant (in adjunctive use), as well as an antianxiety agent. Pharmacokinetically, only Valium provides active *diazepam* as well as the active metabolites 3-hydroxydiazepam, desmethyldiazepam and oxazepam.

But the individual character of Valium is even more apparent clinically than pharmacokinetically. And far more significant. That's because of the patient response obtained with Valium. A response which brings a calmer frame of mind. A response which has a pronounced effect on the somatic symptoms of anxiety, particularly muscular tension. A response which helps the patient feel more like himself again because of the way Valium reduces the overwhelming symptoms of anxiety and psychic tension.

Another important aspect of the clinical character of Valium is safety. Though drowsiness, ataxia and fatigue are possible, these and more serious side effects are rarely a problem. Of course, as with all CNS-acting drugs, patients taking Valium should be cautioned against driving, operating dangerous machinery or the simultaneous ingestion of alcohol.

Unquestionably, many psychotherapeutic agents, including other benzodiazepines, have antianxiety effects. But one fact remains: you get a certain kind of patient response with Valium. It's a response you want. A response you know. A response you trust as part of your overall management of anxiety and psychic tension.

Valium® Ⓘⓥ
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets
a prudent choice in psychic tension and anxiety

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

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Roche Laboratories
Division of Hoffmann-La Roche Inc.
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Contents — August 1979

Volume 62:8
Pages 565-624

COVER WATERCOLOR — "St. Paul Skyline"
E. Theodore Palm, M.D. 575

PRESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association 571

EDITOR'S NOTEBOOK — slanted views
minny 573

PART II — 25 YEARS OF PSYCHOPHARMACOLOGY

25 Years of Psychopharmacology — Part II
F. S. Abuzzahab, Sr., M.D.
Guest Editor 574

New Approaches to the Treatment of Manic Depressive Illness
Edward A. Wolpert, M.D. 576

The Impact of Benzodiazepines on Clinical Practice— Considerations for Therapeutic Use
Rollin M. Gallagher, III, M.D. 580

Drugs and Depression — Tools and Treatments
Leo E. Hollister, M.D. 589

Food and Drug Administration Regulation of Clinical Psychopharmacology
Burtrum C. Schiele, M.D. 593

Future of Psychopharmacology
Nathan S. Kline, M.D. 599

LETTER TO THE EDITOR — Health Care Cost Commission
Brian Anderson, M.D. 611

RHEUMATOLOGY CORNER — Salicylates
Richard B. Tompkins, M.D. 613

PHYSICIANS PHARMACISTS AND REFILLS
Lowell J. Anderson, R.Ph.
Past President, Minnesota State Pharmaceutical Association 615

NEW MMA MEMBERS 617

CONTINUING MEDICAL EDUCATION 579, 596, 617

CLASSIFIED ADVERTISING 620

INDEX TO ADVERTISERS 616

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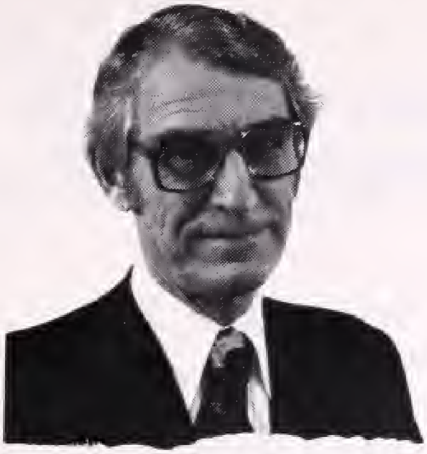

President's Letter

The Federation of Medical Organizations which makes up the AMA is governed in the most democratic way possible in a complex, modern society. And at the state level the business and proceedings of the MMA certainly are conducted in a manner as open as that of any corresponding component society. Yet I sense that we are constantly working in a rather dim light in terms of knowing whether our methods and actions are supported by the majority of the members.

Our nearest approach to full membership participation in the business of MMA is at the annual House of Delegates session. In the period between the annual meeting of the House your officers, trustees, and key persons from the administrative staff gather about once each month to deal with interim business and the details of developing and implementing broad policy decisions made in the House of Delegates. At those times all are acutely aware of the desire that our decisions and actions accurately reflect the needs, the hopes, and the ambitions for the MMA which are held by a majority of its members. It goes without saying that it is of equal concern that our decisions continue to work toward excellent patient care in terms of highest quality at lowest cost.

We all welcome hearing from you by phone or letter to learn how you think MMA could better serve you and society. However, I know of the inertia that must be overcome before one can spend the time and effort to phone or write. Nevertheless, I do wish for your voice to be heard and will attempt to maintain as close communication with each individual member as possible.

For that reason there is included with this page a tear-out, self-addressed postcard which I may from time to time ask you to check the answers to specific questions. At other times it may be blank to allow for your free ranging comment. We will try to always leave sufficient space so that you may ask questions or express individual opinions.

This mechanism for communication carries a price tag. The amount that the system is used will soon let us know if it is worth the cost. I hope that each member will return his/her card this month to let me know if the idea is good and, therefore, deserves a trial. Please tear out the card and mark it for mailing before you turn to the next page.

With warmest regards,

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

See page 617 for list of new MMA members.

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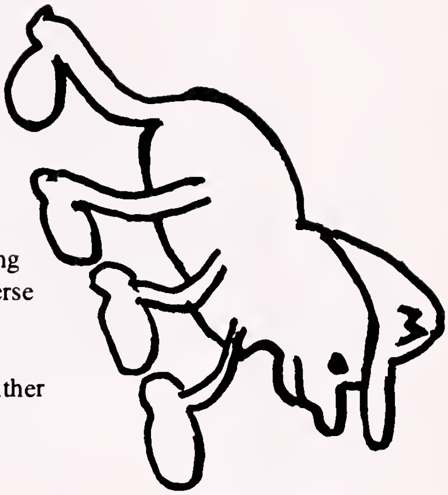
Editor's Notebook

slanted views

dear doctors
my boss the editor
has run off on vacation
after his last editorial
i don t blame him
because a lot of joggers
are in hot pursuit
while he is away
this roach will play
the boss told me
to say whatever
i wanted to say
but he said
keep it short
and talk straight
i informed him
in no uncertain words
i would not
talk straight
because i have
slanted views
on absolutely everything
in this spinning universe
and as for keeping
my poems short
that is no cinch either
because i am
a lively
independent
and free spirit
who leans to the right
and slightly downhill
and who has biased views
on everything that matters
that may be so
he smirked
but i am giving
you only so much
writing room
and before you know it
you will be spaced out
and you will learn
what editorial runoff
is really
all about
minny



25 Years of Psychopharmacology

Special Issue — Part II

F. S. ABUZZAHAB SR., M.D., PH.D.*
Guest Editor

THE 25TH ANNIVERSARY of the introduction of chlorpromazine into psychiatry was celebrated with a symposium on June 4, 1977 co-sponsored by the Hennepin County Psychiatric Society and the Minnesota Academy of Family Practice. The papers presented have appeared in two parts: the February 1979 issue of MINNESOTA MEDICINE covered the articles on "Chlorpromazine's Entrance into Psychiatry — an extremely interesting product," by J. P. Swazey; "Psychopharmacology and Family Practice," by H. Racer; "Impact of Depot Neuroleptics on Psychiatry," by L. Corbett; "Parkinson's Disease, Huntington's Disease and Tardive Dyskinesia — Neurochemical Pathology and Treatment," by E. S. Tolosa; and the "Impact of Psychotropic Drugs on Research in Psychiatry," by J. M. Davis and M. W. Dysken.

Although Cade[1] reported about the use of lithium in controlling mania as early as 1949, the full impact of the treatment of affective disorders was not felt until the neuroleptics had become successful in controlling the symptoms of schizophrenia. This constituted a delay in the acceptance of lithium carbonate by psychiatry. Dr. Edward Wolpert, editor of *Manic-Depressive Illness, History of a Syndrome*,[2] will cover "New Approaches to the Treatment of Manic-Depressive Illness."

As indicated in the introduction to Part I, imipramine was accidentally discovered by Kuhn, in the search for a neuroleptic with possibly less side effects.[3] Although as a general group, the antidepressants have not proven as successful as neuroleptics, their application will be presented by Dr. Leo Hollister as "Drugs and Depression: Tools and Treatment." The latest of Dr. Hollister's prolific list of publications is his book on the *Clinical Pharmacology of Psychotherapeutic Drugs*.[4]

The anti-anxiety agents were introduced in 1955 with meprobamate,[5] which is a member of the propanediol class. It was quickly displaced by the benzodiazepines when chlordiazepoxide was introduced in 1960 and diazepam in 1963. The phenomenal success of these agents in controlling anxiety has led to some controversy about their use in clinical practice. This will be discussed by Dr. Rollin Gallagher in his presentation "The Impact of Benzodiazepines on Clinical Practice — Considerations for Therapeutic Use."

The success of the psychopharmacological agents has called for some federal control over the prescription of benzodiazepines and some guidelines regarding pre-marketing research to prove the effectiveness of these drugs. Dr. Burtrum Schiele, past chairman of the Psychopharmacological Agents Advisory Committee of the Food and Drug Administration and co-editor of *Establishing the Efficacy of Psychotropic Drugs*[6] will cover the area of "Food and Drug Administration Regulation of Clinical Psychopharmacology."

Although the major advances in psychopharmacology have occurred through serendipity, research has widened the base of knowledge about the function of the brain. Dr. Nathan Kline whose name has been intimately related with the field of psychopharmacology, and who is co-editor of *Psychotropic Drugs in the Year 2000*,[7] will present "The Future of Psychopharmacology."

The benzodiazepines have a high degree of patient acceptance, to the point that they can completely displace the physician. This has split the physicians into two opposing camps. One school of thought advocates individual counseling and psychotherapy as the treatment for uncontrollable anxiety. The other group continues to feel that these drugs are very effective, which has led to their world-wide acceptance.

The benzodiazepines have been the subject of illicit use due to their cross-physical tolerance to other central nervous system depressants, mainly in mixed drug abusers. Clinical cases of dependence, however, are extremely rare, about one case per 50 million patient months,[8] unless patients have a past history of drug dependence and shift their dependence to the benzodiazepines. Compared to other central nervous system depressants, the benzodiazepines themselves have a relatively low potential to cause dependence.[8]

---

*Clinical Associate Professor, Departments of Psychiatry, Pharmacology and Family Practice, University of Minnesota Hospitals, Minneapolis, Minnesota and President, Hennepin County Psychiatric Society.

The physical withdrawal symptoms from therapeutic doses of benzodiazepines have been confused with the underlying pre-existing anxiety which was well-controlled by these agents.[9,10]

Parallel to the success of the benzodiazepines has been the growth of consumerism. Although benzodiazepines may produce dependence in individuals in extremely rare occasions, physicians are blamed across the board for excessive prescribing of these agents. A vociferous group in the drug and alcohol dependency field have criticized the prescribing of all mood altering substances in an effort to control drug abuse. The informed public, however, is misled by these mis-directed efforts, since the three evils of our society — alcohol, nicotine, and marijuana — remain uncontrollable.

The neuroleptics have changed the practice of clinical psychiatry and are used in research as tools to unlock the secrets of the brain. The benzodiazepines have had a similar role. Recently the discovery of specific benzodiazepine receptors in the mammalian brain[12,13] has stimulated research for the natural endogenous ligand for these benzodiazepine receptors.[14]

Certain types of anxiety proneness seem to be genetically pre-determined. Since the gene cannot pass the expression of a trait to the progeny unless it is chemically mediated, in the future we will undoubtedly witness a new class of compounds which might even displace the benzodiazepines, just as the latter have displaced the propanediols and the barbiturates.

Finally, a sober, well-balanced attitude towards psychoactive medications is needed. The effectiveness of benzodiazepines far outweighs the potential risk of dependence in the overwhelming majority of patients. Nevertheless, in the future when patient package inserts are a reality, they should include a fore-warning about potential risk of dependency. It is only in this manner that both the physicians' and the patients' interests will be properly served.

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Cover Watercolor

"St. Paul Skyline"

Dr. E. Theodore Palm, Minneapolis surgeon, is the artist of the beautiful watercolor on this month's cover. He was also the artist of the Minneapolis skyline appearing on the February cover of MINNESOTA MEDICINE.

Doctor Palm is on the staffs of Fairview Southdale, Metropolitan Medical Center, and Methodist Hospital. He is a graduate of Gustavus Adolphus College and the University of Minnesota Medical School. He studied art at the Minneapolis School of Art.

New Approaches to the Treatment of Manic Depressive Illness*

EDWARD A. WOLPERT, M.D., PH.D†

Manic depressive illness has been viewed, against the historical backdrop, as an actual neurosis, genetically controlled, in which a biochemical abnormality is reversed by lithium carbonate but in which psychological treatment may be necessary to remove the psychological trigger that sets off the cycle. Some practical problems in the management of the disorder are discussed, and approaches to their resolution indicated.

To UNDERSTAND AND treat manic depressive illness the practitioner needs to appreciate how physicians have viewed the illness over the years and to integrate these views with more recent research findings. At the turn of the century Kraepelin described in detail cases of affective illness and differentiated subvarieties: patients who only had manias, patients who only had depressions, patients who had manias and depressions, patients who had mild cases as opposed to the very severe cases requiring hospitalization, involutional melancholia, and many others. By 1921 Kraepelin[1] had come to the conclusion that all were basically the same illness: patients who came into the psychiatric hospitals of his day with an affective disorder, regardless of the form it took symptom-wise, had a good prognosis and would be able to leave the hospital whereas all other patients — schizophrenics, organic brain syndromes, leuetics — had a poor prognosis and would probably need custodial care interminably.

Abraham[2], the first psychoanalyst to investigate depressive illness, accepted the Kraepelinian nosology and formulated the general dynamics of depression based on Kraepelin's idea that all depressions are essentially the same. Abraham used as his clinical material six patients whom he studied intensively, only two of whom were manic depressive in our sense of the term; the remainder were depressives of various other types. His original formulation stated that in depression the patient is overwhelmed by his complexes, and unable to function; in mania the patient throws off the complexes that have bothered him and is able to function only too well. In his last communication on manic depressive illness Abraham[3] named five factors, all of which have to be present for manic depressive illness to develop: (1) a constitutional accentuation of oral eroticism, (2) a special fixation of the libido at the oral level, (3) a severe injury to infantile narcissism, (4) occurrence of the injury before oedipal conflict resolution, and (5) a repetition of the primary disappointment later in life.

Freud[4] conceptualized depression as resulting from the introjection of an ambivalently held object that has been lost. The superego rails at the lost object, but since the object is now inside the ego, as it were, the ego itself is the subject of the hostility and in response the patient acts depressed. The release of the ego from the bonds of the superego by mechanisms not specified leads to mania. However, Freud was not as sure as Abraham that all depressed patients were the same, and he noted that there were manic depressive patients in whom a lost object cannot be identified either in reality or in fantasy. Those patients in whom losses were present were said to have "psychogenic" episodes; those without losses were said to have "spontaneous" episodes. Most patients have both types. Freud felt that the "spontaneous" episode was neurophysiological in nature, and in 1918[5] stated that at the basis of every psychological illness there was a neurophysiological substrate which he called the "actual neurosis." The psychoneuroses were the psychological consequences of conflict while the actual neuroses represented the direct effect upon psychological representations of dammed up libido or psychic energy, and as such were physiological disorders. Most later analytic writers state that despite the dynamics present in each case, to fully understand the disorder one must understand what was occurring on a neurophysiological level, but neurophysiology did not yet have the answer.

---

*From the Michael Reese Hospital study of manic depressive illness. Supported in part by a grant from Mr. and Mrs A. Frank Rothschild, Sr.

†Director, Clinical Services, Institute for Psychosomatic and Psychiatric Research and Training, Michael Reese Hospital and Medical Center and Clinical Professor of Psychiatry, Pritzker School of Medicine, University of Chicago. Consultant, Sonia Shankman Orthogenic School of the University of Chicago.

Presented at the Symposium on 25 Years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

Reprint address: Edward A. Wolpert, M.D., PhD., Director, Clinical Services, P&PI, Michael Reese Hospital and Medical Center, 2959 South Ellis Avenue, Chicago, Illinois 60616.

Feinstein and Wolpert[6], in presenting a case of juvenile manic depressive illness in 1973, felt that:

> The affective systems of patients with manic depressive illness may have a basic vulnerability which, when overstimulated, begins a discharge pattern which does not easily lend itself to autonomous emotional control. Some biochemical variation, possibly on a genetic basis, leaves the affective system with a specific vulnerability to affective stress.

Freida Fromm-Reichmann and her group[7] studied twelve cases of manic depressive illness and found a specific familial configuration in the manic depressive: one parent felt warmly towards the child whom it valued but was seen by the child as a failure; the other driving, successful parent did not feel warmly towards the child but pushed him or her onwards to value abstract "success." The child was made to shoulder the burden of the family's upward, socially mobile aspirations. This work, done on relatively wealthy private patients, was confirmed later by work done by Gibson et al.[8] with lower middle class and lower class patients.

It had been known for years that unlike every other psychological illness there was, using the words of the last century, a very clear hereditary "taint" in patients who had manic depressive illnes [e.g., (1)]. Study after study demonstrated an increased incidence of depressive-like illness or alcoholism in the families of manic depressives. More recent studies, including use of genetic markers where available have been summarized by Tsuang[9]. These studies suggest two possible genetic modes of transmission of what is now known as recurrent bipolar affective disorder: an X-linked and a non-X-linked mechanism. Most exciting is recent work indicating that an RBC membrane transport system for lithium[10] may be under genetic control[11].

Manic depressive illness has been found to differ from other depressive illnesses in a variety of physiological variables [e.g., (13)]. Hartmann[12] studied the all-night electroencephalogram in manic depressives when normal, depressed, and manic, and found that in the depressed phase patients sleep more and dream more than do psychotic depressed patients, normals, or manic depressive patients in the manic phase. The manic patient, on the other hand, had a decreased dream time and decreased sleep time. These EEG findings are similar to illness phase differences found in almost all physiological areas studied.

The manic depressive patient thus demonstrates three distinct psychophysiological states that can be characterized by asking the appropriate anamnestic questions. In one state the patient is depressed. When depressed eating may be variably increased or decreased. Sleep, unlike that of all other types of depression, is characteristically increased but is not refreshing. The sexual drive is vastly decreased and energy available for usual tasks decreased. Typical depressive selfdeprecating ideation is present. In the normal interphase state the manic-depressive has no symptoms. The manic state is characterized by an increase in energy manifested by hyperactivity, in all spheres: increased sexuality, decreased need for sleep, increased ability to work. When this energy becomes too much for the psychic structure to contain, a frank manic episode occurs, with loose and tangential associations, grandiosity, distractibility, attempts to carry out projects that are irrational and cannot be successfully carried out, and sometimes paranoia.

Psychogenic precipitants may sometimes be noted prior to a frank mania. Loss of an object in reality or in fantasy is the most frequent psychogenic precipitant. Physiological precipitants are unknown, but their consequences may be manifest in prodromal symptom-states, in which — by careful examination of the patient's mentation — one can find typical symptoms that presage the onset of either a mania or a depression. In these prodromal states the patient may report either typical dreams or typical sensory experiences during the day. The dreams may be symbolic of an overthrow of the psychic controlling structure, or they may be themselves a frank hyperstimulated state[13].

Thus we have developed the concept that manic depressive illness is not a dynamic illness, as is depression itself generally, but rather it is an actual neurosis in which three divergent psychophysiological states coexist in the same person but are manifested alternately, and that the disorder has a genetic underpinning. What we are describing is a psychoeconomic not a psychodynamic disorder, flourishing within a specific familial configuration, consisting of a potentiality to mood swings that can be activated by psychogenic triggers ("losses") or unknown physiological triggers.

The treatment of manic depressive illness, once confined to sedation and control during mania, protection and alimentation during depression and psychotherapy in the interphase, has changed markedly since Cade serendipitously discovered the efficacy of lithium salts in mania. The resulting literature is too numerous to cite here, but a good review may be found in *Lithium: Its Role In Psychiatric Research and Treatment*[14].

The psychology of the patient as well as the physiology of the patient must be treated. Manic depressive patients do not demonstrate a common unitary psychology; the illness is found in people whose psychology diverges radically. Some patients who otherwise are normal have mood swings of tremendous degree. Patients who are hysteric, schizophrenic, obsessive-compulsive, any of the psychiatric classifications, may have manic depressive illness in addition. Thus the psychology has to be dealt with separately, as it were, from the manic depressive illness proper, and the psychological treatment is that of the psychological problem, whatever its nature. As far as the treatment of the physiological state is concerned, lithium carbonate, when physically safe to use, is the treatment of choice, both in the acute phase of the illness and prophylactically. This recent innovation is also old. The ancient Roman physicians knew that certain springs, known now to be rich in lithium, were efficacious in resolving agitations of various types. In the time of the late Republic and early Empire various patients were sent to these springs to drink the healing waters.

Several biochemical theories have been developed to explain the mechanisms by which lithium works. The norepinephrine theory, which may or may not be true, is useful heuristically to explain how we use lithium. The basic postulate is that increased norepinephrine uptake post-synaptically will lead to a decrease in depression, increased deamination of norepinephrine pre-synaptically will lead to a decrease in mania. Lithium does both selectively. According to this theory when a person in equilibrium is threatened by a mood swing, the brain needs increased lithium. In such a person who suddenly needs more lithium, a given oral dose of lithium will lead to relatively little in the peripheral blood because the brain has taken it from the blood. In a person who needs only a little lithium in the brain, that same given dose of oral lithium will lead to an increase of lithium in the peripheral blood because the brain does not capture much lithium. Therefore, in acute mania, one uses as much oral lithium as one needs until the serum lithium level rises, side effects occur, or mania decreases. Once the mania decreases one must carefully decrease the oral lithium as the blood level will rise as the mania is controlled. In a few patients we did balance studies indicating lithium retention early in a manic episode and increased excretion later in the manic episode. In the chronic state between episodes one gives enough oral lithium to keep the blood level somewhere in what is called the therapeutic range, usually said to fall between 0.6 meq/L and 1.1 meq/L, without causing uncomfortable side effects. Whenever typical prodromal symptoms occur, increased lithium is prescribed to control the impending mania, and in such a state much increased oral lithium does not lead to a proportionately increased serum lithium level.

Lithium is toxic to the myocardium, to the thyroid, to the proximal convoluted tubule of the kidney, and to the brain, and therefore it is critical to evaluate these systems before beginning treatment. If difficulties are found in these organ systems, the physician must responsibly determine which is the greater danger to the patient — the increased organ damage that might result from the use of the lithium or the disadvantages in not using the lithium in the treatment of the underlying illness.

Moreover, there are some complications to watch for very carefully during treatment with lithium. The easiest to control are the rashes that are seen in patients who are on lithium. Usually these rashes respond to changing from one preparation to another because each of the capsular materials that contain the lithium are made out of different material and a fair number of people turn out to be allergic to one or the other of the capsules but not to all. There is even a tablet so one can give the tablet alone without the extra capsular material. Rarely, patients do indeed have a skin reaction to lithium itself. Then one must decide which is worse — the possibility of a manic episode or the skin reaction.

Hypothyroidism is a very frequent complication in patients on lithium treatment for manic depressive illness, probably because there are many undiagnosed cases of thyroiditis in which thyroid function is compromised and lithium compromises it further. Excessive weight gain is sometimes a problem for patients. In some of these patients nothing except taking the patient off lithium will stop the weight gain. Lithium induced nephrogenic diabetes insipidus is unusual but not rare. Lithium induced interstitial nephritis is a possible complication, most usual following gross toxicity.

The usual symptoms of lithium toxicity at the low blood levels — which are really side effects and only disturbing because they may disturb the patient — are tremors, diarrhea, nausea. When the side effects become dangerous the patient may have visual disturbances, sometimes delusions or hallucinations, and in extreme cases cardiorespiratory collapse. One cannot count on the blood levels as being the last arbiters of the state of the patient; a complete clinical evaluation is more important than an isolated blood value. We recently reported a case in which panhyperarousal in an impending mania was associated with a serum lithium level of 4.5 meq/L, but no other abnormality[15].

We[16,17] are presently reviewing our ten years' experience with the treatment of manic depressive illness by private practitioners. What is becoming clear is that once lithium has controlled the acute episode and we are able to prevent major recurrences, some of our patients need little or no further psychotherapy. Others however, once the major mood swings are controlled, are revealed to have additional major psychological pathology requiring further treatment, ranging from psychoanalysis to psychotherapy. Some of our patients need an intensive psychological approach to help them not manipulate themselves into mania by abusing their knowledge of lithium. Many need close supportive follow-up to control minor recurrences of mood swings with briefly increased lithium dosage. Resolving psychological conflicts by psychotherapy removes the trigger of psychogenic episodes. The treatment failures we see are either because the physician does not treat the psychological picture decisively, or because he does not seem able to respond quickly and flexibly enough with adjustments of lithium when the physiological picture changes.

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Continuing Medical Education

August 22, 1979 — Hennepin County Medical Center

Sleep Disorders in Clinical Medicine, Hennepin County Medical Center, Minneapolis. Sponsor: University of Minnesota 612-373-8012.

September 13, 1979 — Mercy Medical Center

Symposium — Problem Oriented Record Keeping, Mercy Medical Center Auditorium, Coon Rapids. Sponsor: Health Central Inc. (Mercy Medical Center, Unity Hospital, Golden Valley Health Center) Contact: Joseph Cardamore, M.D.

The Impact of Benzodiazepines on Clinical Practice

Considerations for Therapeutic Use

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The benzodiazepines are widely and, in general, appropriately used by physicians for many conditions. Sociocultural and epidemiological factors, as well as the pharmacological properties of the drugs themselves — clinical effectiveness, high margin of safety, and few untoward reactions — account for this wide use. Clinicians need to carefully consider indications, dosage schedules, and implications of long-term use when prescribing these medications for anxiety, sleep, and other conditions.

DISCUSSION OF the use of psychotropic drugs in general, and the anti-anxiety agents, including benzodiazepines, in particular, is no longer limited to medical schools, physicians and professional journals. Indeed, one of the most comprehensive essays on this problem, "Valiumania"[1] appeared in the New York Times Magazine. What is everybody talking about?

Clinicians hear, "Can't you just give me something for my nerves?"; "I don't want to become a drug addict;" I don't believe in drugs;" "I need a refill, doc." At public forums, a general charge is aired that we are living in a grossly over-medicated society in which the prescribing of psychotropic medications is contributing substantially to problems of drug abuse and erosion of social character. Physicians are accused to being everything from the architects of a general plot, to unwilling accomplices of the drug companies.

Since the arguments pro and con the use of psychotropic medication contain personal prejudice, subjective impressions, socio-political identification, or simplistic deductions arising from drug consumption figures, we will review some of the data available.

Epidemiological Data

Balter[2] from NIMH reported some data from four sources: 800 U.S. drug stores, a panel of 500 physicians in 27 U.S. cities, a national sample of physicians in private practice, and a national household survey with in-depth interviews of over 2500 people. These data are summarized in Tables 1, 2, and 3.

The following observations can be made:

Prescription rate for psychotropic drugs increased 44% from 1964-1972 whereas prescriptions for all drugs increased by 61% (Table 1).

Despite allegations of chronic users, relatively few adults (5%) have ever used psychotropics on a long-term basis (Table 1).

TABLE 1

Extent of Use of Psychotropic Drugs

A. Prescriptions Written 1972
   1. Total — 1,400,000,000
   2. Psychotropics = 215,000,000 (16%)
   3. Antianxiety = 94,600,000 (7%)

B. Increase in Prescription Rate
   1958-1964 Psychotropics > total drugs
   1964-1972 Psychotropics < total drugs

C. Extent of Use, Adult Population (1 or more)

Patterns of Use:	Once or More	> 6 Months
Women =	29%	7%
Men =	13%	4%
All Adults	22%	5%

TABLE 2

Prescribing Data on Psychotropic Drugs

1. Physician Group	% of New Prescriptions
General Practitioners	50%
Psychiatrists, Neurologists	5%

2. Drug Group	% With No Refills	Duration of Therapy	
		< 1 month	> 1 month
Short-acting barbiturates	71%	Not reported	
Amphetamines	76%	64%	80%
Antianxiety agents	60%	60%	89%

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The majority of prescriptions for psychotropics are written by non-psychiatrists (Table 2).

The data did not support the contention that drugs were prescribed for long periods with many refills permitted (Table 2).

Only one-third of the cases of new therapy directed treatment to a person with a specific diagnosis of a mental disorder. It was clear, however, that the specific therapeutic intent was to alleviate symptoms of psychic or emotional distress in most instances. Investigation of the use of medications in response to life crises and distress in general revealed that Americans have strong reservations about using psychotropic drugs, and that those who used them generally have substantial provocation as evidenced by their high level of psychic distress and life crisis (Table 3).

TABLE 3

Symptoms, Life Crises, and Psychotropic Drug Use

	% with high scores on indices of psychic distress and/or life crisis		% with low scores on both indices
	Men	Women	Men & Women
All drug users	60%	70%	16%
Drug users 2 months	70%	80%	2-3%

The majority of patients interviewed felt drugs were effective, but had serious qualms about their safety and the desirability of using them to cope with problems. Although the doubts were often expressed in terms of loss of control or interference with problem solving and social functioning, the underlying concerns seemed to be essentially the moral issue of self-reliance and strength of character.

Manheimer et al.[11] surveyed over 2500 people ages 18 to 74, with in-depth interviews and questionnaires, to assess popular attitudes and beliefs about tranquilizers. Their data can be summarized as follows: (1) there is a general belief in the efficacy of medications; (2) there are doubts about the virtues of its use regarding long range physical complications and moral and behavioral consequences; (3) there is a tendency to consider them as symptomatic treatment and as diminishing motivation to change; (4) they are often seen as a sign of weakness; (5) the attitude that mental illness equals moral weakness is correlated with a negative attitude toward anti-anxiety agents.

Role of Primary Care Physician

This data raises several questions about the role of the primary care physician in the epidemiology of drug use. Traditionally the physician has been perceived by the public as a provider of solace and comfort to the ill, a reassuring parental figure with the bedside artistry able to see a family through the worst crisis. A study by Lee[3] showed that people continued to seek help for psychological problems from family physicians, particularly in rural areas, and despite advances in psychiatry and the development of the community mental health movement.

An aroused interest and public demand for psychiatric service from family physicians have resulted from two phenomena, as reported by Whittkower:[5] (1) rapid advances in psychiatry; (2) fragmentation of medical care resulting from increased specialization, perceived by the patient as a need for an integrative approach to his problems.

Stepansky[4] noted that there is an increase in chronic conditions requiring major psychosocial adjustments. Patients with medical problems such as diabetes, arthritis, cancer, and heart disease have improved survival rates, necessitating long term care outside of a hospital. Chronic care institutions, responding to advances in psychopharmacology as well as to changes in the socio-political climate as reflected in the legislation and legal decisions, have increasingly turned out patients with chronic psychiatric conditions to be cared for in the community by family physicians.

Psychotropic drugs have become the predominant mode of treatment of psychiatric disorders by family physicians, relegating psychotherapy to a secondary status.[4] Unlike many of the other treatment modalities available for non-psychiatric problems, psychotropic medication is relatively "brand new" medicine, coming after the majority of practicing physicians have been through medical school. Indeed, Herman[6] reviewed the sources of drug information utilized by physicians, and noted that since most physicians did not have access to complete and objective information on prescription drugs, many resorted to use of commercial resources. Continuing medical education and professional conferences are increasing sources of information.

History of Anti-anxiety Agents

In 1955, Dr. Berger at Wallace Laboratories discovered meprobamate, a propanediol, which instantly became a "hit." With improved mass media communication, its tradename "Miltown" became a household word. Indeed, a famous comedian at the time added "W" to his first name and called himself "Miltown" Berle!

Two benzodiazepines, chlordiazepoxide, then diazepam were soon introduced by Roche — leaving meprobamate far behind. These two classes of medications, the substituted propanediols and the benzodiazepines, were warmly embraced by the medical profession and the public as the answer to their anxieties, which heretofore had been treatable only with expensive and exclusive psychoanalysis.

There are several reasons proposed for this shift.[1,15,16] Anthropologists have traced the use of mood altering drugs, particularly alcohol, back to pre-history when the first cave man drank fermented grain or fruit juice, or picked the "right" wild mushroom. Since then, in what Gerald Klerman euphemistically calls "psychotropic hedonism," there have been many intermediate steps leading up to "diazepam mania." Indeed, one of our famous progenitors Sigmund Freud himself, was apparently "Hooked" on cocaine. Sociologists might claim that it is the deeply ingrained American faith in technology which turns us on to medications rather than to exploration of feelings: "STP for the smooth running of your car, diazepam for the smooth running of your life."

Others espouse a medical economics theory. Physicians who deal with life-threatening illnesses are trained with specific skills to carry out their treatment rapidly and effectively; they have been taught few skills to handle the vague and oftentimes apparently non-life threatening symptoms of anxiety. The psychotherapeutic approach takes time and energy, neither of which the physician has after seeing 40 patients in a morning. Indeed, Dr. Robert Moses, editor of JAMA, has noted that physicians prescribe more psychotropic medications as the day wears on.

There is much more evidence, however, to support the contention of psychopharmacologists and the pharmaceutical industry that it is the ability of the psychotropic drugs to meet the patients' needs that is responsible for the increased use. The drugs work. They relieve anxiety safely, and they produce grateful patients. What more could a physician ask of a medication?

Questions of overuse, misuse and abuse of diazepam have been raised. The popularity of diazepam makes the question of overuse pertinent, suggests Sidney Cohen, former director of Division of Narcotics Addiction and Drug Abuse at Nimh.[12]

Misuse of prescriptions of diazepam is treated separately in the section on clinical applications.

Abuse is a question, since street supplies of diazepam have become substantive, as evidenced by the number of "drug mentions" in crisis center and emergency room reports, constituting about 10% of all drug mentions.[12]

To further assess abuse, it would be useful to know what the users of diazepam would be doing if they didn't have diazepam. If they preferred them to the use of barbiturates, then diazepam use is much safer. If they would use no other drug, then its abuse is certainly undesirable. Another measure of abuse is the ratio between legitimate prescriptions written and the number of "mentions" of the use of the drug by the Drug Abuse Warning Network. Diazepam has approximately the same ratio as other medications of its class.

Pharmacology and Therapeutics of Diazepam

The following discussion of the pharmacology and therapeutics of benzodiazepines expands on literature by Shader and Greenblatt,[13,14,19,21] Hollister,[15,16] and others.[17,18,26]

Pharmacologic Properties

Diazepam and chlordiazepoxide, as opposed to oxazepam, have a prolonged half-life, particularly in the elderly and those with liver disease.[22] The clinical implications are that they can be given once a day, usually at bedtime so the sedative actions will be helpful for sleep and the anti-anxiety actions will be present during the following day. Accumulation can occur, and can be a problem in conditions such as the treatment of alcohol withdrawal where large doses are employed. They are not potent inducers of drug metabolizing enzymes in comparison with other drugs of their class and, therefore, doses can remain steady and addiction potential is decreased. Absorption is more rapid and predictable by oral route and thus they should not be used intramuscularly where absorption is unpredictable and accumulation a potential problem.

Hollister[16] has compared the pharmacological properties of all the anti-anxiety drugs, rating them on nine parameters of safety, side effects, and clinical efficacy. His data show the benzodiazepines to be clearly superior to the others.

Mode and Site of Action

The site of action is unknown, but there are indications that the benzodiazepines act on the limbic system and, in particular, the amygdaloid nuclei. Recent literature[23-25] speculates on the different possible neurochemical actions of these drugs as they produce their specific but separate sedative, anti-anxiety, muscle relaxant, and anticonvulsant clinical effects.

There is evidence that diazepam produces both central and peripheral muscle relaxation, which accounts for its popularity among physicians for the relief of muscle tension and spasm, whatever the etiology. These drugs also have anticonvulsant effects, and diazepam is routinely used for status epilepticus. A recent article by Lasagna[26] reviewed evidence for the support of common clinical usage of benzodiazepines in psychophysiologic disorders, including hypertension, G.I. disturbances, and cardiovascular problems.

Untoward Effects

Benzodiazepines have shown potential for depressing respiration and circulation, although certainly in much relatively higher doses in relation to their therapeutic effect than other sedative/hypnotics. Although initially described as without addiction potential, there have been increasing reports in the literature about withdrawal reactions to the benzodiazepines after prolonged usage of high doses. Paradoxical rage reactions, where diazepam "disinhibits" repressed hostility, have been mentioned. Cross addiction with alcohol remains a problem.

Clinical Use

A. Anxiety

Benzodiazepines are not a panacea for society's ills, but instead a very effective medication with a high degree of safety when used appropriately. Several interesting studies have looked at more specifically the metapharmacological variables involved in the treatment with benzodiazepines. Rickels[17] studied how patient's response to medications correlated with other factors. One four week study of the 169 outpatients treated with meprobamate, chlordiazepoxide or placebo showed no significant difference between the treatment, but that the major influence on treatment response was the non-specific factor, "Dr. Warmth."

The Figure represents the effect of treatment setting on medication response in a study of 472 anxious outpatients given diazepam, phenobarbital, and placebo.

The non-specific factor "treatment setting" was found to be at least as improtant for treatment outcome as the specific active medications, which did produce significantly more improvement than placebos.

One can only speculate why in the general practice setting there was the most favorable response to medications but the least favorable to placebo. It certainly suggests that if the physician "believes" in the efficacy of the medication, it may indeed prove more efficacious. Analytic training and a possible reluctance to "rely" on the medication may explain the poorer response to benzodiazepines in the psychiatric practice, whereas lack of other "treatment skills" would tend to explain the general practice setting's inability to treat symptoms with placebo.

These investigators went on to study the relationship between improvement with benzodiazepines and other factors.

Their study, although the numbers were small, certainly suggests that there is room for further clinical investigation of some of the differential predictors of response to the various anti-anxiety medications, and amongst the benzodiazepines themselves.

Hollister[15] suggests that patients with characteristics of extroversion and physical activity ("doers") tend to respond to anti-anxiety drugs with increased anxiety. Patients who are intellectual, passive and esthetically inclined ("thinkers") seem to tolerate the drugs well and find them beneficial. Thus, the anti-anxiety drugs may immobilize one of the defenses against anxiety that the particular personality may need, and such patients might be better treated with smaller doses or with no drugs at all.

When clinicians consider indications for benzodiazepines, it is useful to try to distinguish the various types of anxiety which they encounter clinically, and develop some general guidelines as to the appropriateness of using medications.[14]

Situational Anxiety

These reactions are to a diversity of stressful stimuli and are usually short-lived, ending once the experience is completed. Supportive discussions and rehearsals are usually effective. Examples include preparation for surgery by discussion with anesthesiologists, role playing and assertiveness training in preparation for job interviews. Medications can be used temporarily if the former do not suffice.

Phobic Anxiety

If etiology of the phobia is straightforward, resulting from a traumatic experience, systematic desensitization is probably the treatment of choice. Other more complex phobias usually require an eclectic approach

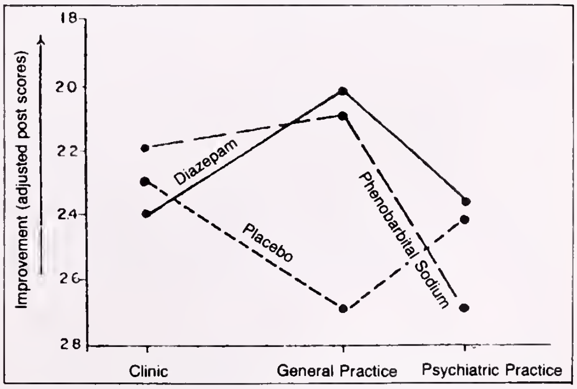

Figure — Treatment setting and drug response (N = 322).

including desensitization, psychotherapy, and pharmacotherapy.

Anticipatory Anxiety

Anticipatory feelings may represent fears of anxiety states associated with situations or dreaded objects. Again, an eclectic approach is useful.

Free Floating Anxiety

Oftentimes this is episodic in response to not clearly defined internal stimuli, and if there is no associated psychotic depression, will respond to episodic use of benzodiazepines.

Traumatic Anxiety

Ventilation and "working through" grief are important. It is crucial that the physician rule out other post-traumatic medical/surgical conditions before the judicious prescription of anti-anxiety agents, as well as rest and removal from stress.

Anxious Depression

Benzodiazepines can be useful in those depressed patients who seem to have anxiety symptoms preceding onset of depressive symptoms, when there are not clear cut indications for antidepressant medications. They can often help with the sleep onset disturbance in these states.

Anxiety in Medical Conditions

Treatment should be directed at the underlying medical condition, but there is much evidence to support the use of benzodiazepines in those conditions in which stress may be a factor, including dermatological conditions, cardiovascular and G.I. disturbances. These may be helped in the absence of overt and reported anxiety.

The clinician should keep in mind the following principles when prescribing benzodiazepines for anxiety: (1) He should be educated as to their pharmacology and convinced himself of their efficacy. (2) He should spend some time with the patient, and be warm, empathic, and enthusiastic about the treatment methodology. (3) He should assess the patient's attitudes towards medications in general, and the anti-anxiety medications in particular. If there is a negative moralistic attitude towards psychotropic drugs, he should reconsider their use, and perhaps spend more time in patient education, and possibly in exploration of "hang-ups" about obtaining medical treatment. (4) Dosages of benzodiazepines should be titrated against the patient's needs for relief of symptoms versus the side effects of sedation and potential impairment which might affect his employment status and his defenses. There is no doubt that patients vary widely in their dosage requirements, and for this reason, the patients should be cautioned to take initial dosages at night when at home when there is little danger of complications arising from sedative effects. Hollister recommends an initial dose of 2.5 mg of diazepam three hours before bedtime, to be doubled every night until the three criteria indicating clinically effective blood levels are attained: enforced sleep, a good night's sleep, and a slight hangover upon awakening (indicating anti-anxiety levels for the daytime). More than 20 mg daily suggests that tolerance has developed secondary to concurrent ETOH or other tranquilizer use. (5) This point has been controversial among psychiatrists, but there is little evidence to support the contention that the anti-anxiety effects of benzodiazepine interfere at all with the beneficial process of psychotherapy. Patients should be encouraged to learn new coping styles and strategies to deal with ongoing stresses in their lives. Physicians should be comfortable with providing some form of psychotherapy or referring patients to someone who will provide this kind of treatment. Rigidity about either treatment modality will only hurt the patient. (6) Except when using oxazepam, a single hs dose of benzodiazepine, because of long half-life, is sufficient. Accumulation can be a problem. (7) Patient education about the following can greatly assist the clinician in obtaining effective compliance and intelligent use of medications: (a) Anxiety generally has an episodic, fluctuating course in response to stress, both environmental and psychological, and medications should therefore be used episodically, perhaps one to two weeks at a time; (b) medications are no substitute for development of adequate coping strategies for life problems; (c) follow up visits to assess clinical efficacy, like for any other drug are essential; (d) a record of medication uses is helpful — medication cards can simplify compliance. (8) Long-term refillable prescriptions should not be used.

Sleep Disorders

In recent years, flurazepam hydrochloride (Dalmane) has become increasingly popular as an hypnotic agent. Again, as with anxiety, it is important to thoroughly assess the five major underlying causes of insomnia — situational factors, medical conditions, psychological factors, drug withdrawal, and aging. Thus, anti-depressant medication, pain medication, behavioral modification and appropriate withdrawal schedules, are often necessary along with the prescription of hypnotic drugs. When hypnotics are indicated, flurazepam has significant advantages over other hypnotic agents,[21] including the following: (1)

Flurazepam is as effective as other hypnotic drugs in short-term controlled studies, and its efficacy persists up to 30 days in longer-term studies, while other hypnotics become ineffective. (2) It has relatively minor effects upon REM sleep and does not produce REM rebound on withdrawal. This may diminish the likelihood of drug dependence. (3) Flurazepam does not cause enzyme induction and has little abuse potential.

Clinical Use

Kales et al.[18] has recommended the following guidelines for the use of flurazepam for sleep disorders: (1) The physician should know that maximum effects of flurazepam do not occur on the first night of drug administration, but usually by the second or third nights, and this information should be conveyed to the patients to prevent them from becoming discouraged prior to the drug reaching maximal effectiveness. (2) An initial dosage of 15 mg hs, should be continued for at least one week and usually for two weeks. If not effective during this time, when the active metabolites will be accumulating, dosage should be increased to 30 mg hs. (3) The gradually accumulating levels of metabolites and consequent carry-over drug effectiveness from one day to the next are also relevant to possible effects of flurazepam on daytime performance. Therefore a small initial dose will allow the physician to monitor these effects. (4) Because of carry-over effectiveness of the active metabolites of flurazepam, drug holidays are encouraged, but will not diminish the effectiveness of flurazepam in inducing sleep. A suggested schedule would be prescribing the drug for nightly use during the week and allowing the drug holiday on weekends. Stress management, relaxation, and behavioral techniques should be utilized when possible to minimize long-term use.

Other Disorders

The clinical use of benzodiazepines for neuromuscular diseases, seizures, alcohol withdrawal, and anesthesia has been summarized well in other publications.[13,19,20]

Conclusion

The benzodiazepines' wide use in many conditions, is a result of their clinical effectiveness and their high margin of safety, with few untoward reactions. Sociocultural factors have also had an impact. It behooves the medical profession to effectively educate themselves about the proper indications and use of these drugs so that not only do their patients get the most benefit, but in addition, so that society does not unnecessarily restrict the physician's use of these highly effective medications. This does not imply that we should not continue to seek out alternative and more ideal methodologies for the treatment of anxiety and other disorders now effectively treated by benzodiazepines, and to seek out more specific differences in the clinical efficacy of these drugs themselves. Psychosomatic techniques such as relaxation exercises and transcendental meditation certainly have a place in the long-term management of these conditons, and their effectiveness and use with and without medications need to be explored in the future.

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Drugs and Depression

Tools and Treatments

LEO E. HOLLISTER, M.D.*

The current concept of the biochemical pathogenesis of endogenous depression, the so-called "amine hypothesis," stems directly from the reserpine-induced model of depression. Postulating a deficiency of biogenic amines in depression from this model led to the use of monoamine oxidase inhibitors as antidepressants. The fortuitous discovery of imipramine as an antidepressant led to the concept of the "amine pump." Discovery that tricyclics differed in their action on the amine pump in regard to specific neurotransmitters suggested that more than one kind of disorder of biogenic amines might be present. Thus, we use drugs to provide clues to the nature of the disorder that we often treat with the same drugs.

THE MODERN ERA of psychopharmacology has provided not only drugs that alleviate the misery of emotional disorders, but ways to learn more about their pathogenesis. We hope soon to be able to develop drugs based upon a better understanding of what ails our patients rather than simple good fortune.

The Model of Depression

Early in its use, reserpine, one of the first drugs of this era, proved that it could make otherwise normal persons depressed. A dose of 1 mg daily for seven days made seven of 19 normal volunteers depressed, while none of 20 subjects who received placebo became depressed.[1] A sizable number of persons seem to be vulnerable to drug-induced depression, just as they are to depressive illness.

As the mode of action of reserpine was elucidated in pharmacological laboratories during the 1950s, it became apparent that the drug blocked the storage of neurotransmitters in nerve endings, creating a deficiency. Serotonin was first discovered to be affected, but later norepinephrine and dopamine were also found to be involved. The logical sequence was completed by concluding that depressed states might be associated with a decrease in available neurotransmitters, especially the biogenic amines. By the late 1950s, therefore, the amine hypothesis of depression could be proposed, largely on the basis of drug actions.[2]

Antidepressant Drugs

The appreciation that biogenic amine deficiency might underly depressions and that these amines were largely catabolized by monoamine oxidase (MAO) led to laboratory investigation of inhibitors of this enzyme.[3] One of the most potent was iproniazid, the original hydradize antimycobacterial drug. One of its side effects in tubercular patients was euphoria. It was studied clinically and found to be effective. On the other hand, a supposed variant of the tricyclic phenothiazine structure, imipramine, was fortuitously discovered to be an antidepressant. Its mode of action was not immediately clear. Later it became known that imipramine and related drugs blocked the uptake of released biogenic amines in the synapse, prolonging their action and presumably making up for the postulated deficiency of released neurotransmitter. Both types of antidepressants, the tricyclics and MAO inhibitors, were eagerly embraced by clinicians as pharmacological substitutes for electroconvulsive therapy, the only effective treatment then available for severe depression.

Heterogeneity of Depression

Although experience with antidepressants in depressed individuals confirmed their favorable effects, it was much more difficult to prove in controlled trials that they were superior to placebo. Such trials were generally conducted using unselected cases of depression. Attempts to refine the clinical nosology of depression using computer techniques clearly established that so-called antidepressant drugs were effective only in a small proportion of depressed patients, those with motor retardation or thought disturbances.[4] Such depressions were the type which had previously been termed endogenous or "vital", the latter term referring to the disturbances of appetite, sleep, sexual drive and motor activity so characteristic of this type of depression.

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Presented at the Symposium on 25 Years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

Although a variety of terminology has been used to describe depressive disorders, I still prefer the endogenous-reactive dichotomy as it implies etiology. When samples of patients with true endogenous depression are studied the superiority of tricyclic antidepressant drugs over placebos is more readily apparent. On the other hand, patients with reactive depression react nonspecifically to treatment, whether it be supportive psychotherapy or a variety of drugs. including tricyclic antidepressants. The distinction between the two types of disorders has implications both for current treatment as well as future prognosis.

Although the depressive phase of manic-depressive disorder is often indistinguishable clinically from endogenous depression, other characteristics of this disorder allow distinctions to be made. Its genetic transmission is markedly different from that of endogenous depression; reactive depressions are assumed to have no genetic component. The unfortunate resurrection of the term "bipolar" to describe this manic-depressive disorder has created confusion in making distinctions between endogenous depression and manic-depressive disorders. Manic-depressive disorder responds best to lithium treatment, although the depressive phase may require concurrent antidepressants just as the manic phase requires concurrent antipsychotics.

Effective drug treatment has compelled clinicians to make clearer diagnostic distinctions between the various affective disorders. Unfortunately, clinical distinctions, even the best possible, have not alone provided clues to the pathogenesis of these disorders.

Pharmacologic Actions of Tricyclic Antidepressants

Tricyclic antidepressants have three main pharmacologic actions. First, they are sedative rather than stimulant drugs. Sedation is most evident in non-depressed persons and less so in depressions, especially those of the agitated type. The type of sedation is more like that of phenothiazines than that of the antianxiety drugs, and may be perceived as disagreeable by non-depressed persons. The extent of the contribution of this pharmacologic effect to relief of depression is unknown, but it is probably negligible.

Second, most tricyclic antidepressants have anticholinergic actions. Although this action is most evident in common side effects, such as dry mouth, blurred vision, constipation, difficulty in urination and mental confusion, it may contribute somewhat to the therapeutic action of these drugs. Some recent work, based in part on this sort of speculation, indicates that increasing cholinergic activity may induce depression. Relief of depression by pure anticholinergics, however, has not been really established, although there have been some reports suggesting this.[5] Possibly, anticholinergic action is important mainly when combined with other actions.

The third, and most important, pharmacologic action of tricyclics is their ability to block the uptake of biogenic amine neurotransmitters released in the synapse. This "off-switch" of neurotransmission requires an active pumping mechanism which is impeded by the tricyclics. Unfortunately, some drugs highly regarded as antidepressants, such as doxepin, are relatively weak in this action, while others, such as iprindole, lack it entirely. Thus, one can not be certain that the block of the amine pump is the sole, or even the major, action of these drugs for relief of depression.

Matters became even more complicated some years ago when it was discovered that tricyclics differ in their effects on blocking the amine pump for different neurotransmitters.[6] Tertiary amine tricyclics, exemplified primarily by amitriptyline (imipramine is also an example, but it is metabolized *in vivo* largely to its secondary amine metabolite, desipramine), block selectively the uptake of serotonin. Secondary amines, such as desipramine and nortriptyline, selectively block uptake of norepinephrine. The clinical experience that some patients might respond to one drug and not to another could possibly be explained by the fact that the drugs were not equivalent. By implication, endogenous depressions were not equivalent either.

Amine Hypothesis Revisited

As originally conceived, the amine hypothesis of depression postulated a deficiency of either serotonin or norepinephrine transmission in the central nervous system. For a long while, the relative importance of the two neurotransmitters was debated. Rather than simply one or the other being important, both might be, but in different types of depression, or both might work together.

Recent work, far too preliminary to be accepted as verified, suggests that both neurotransmitters are important. Attempts to prove norepinephrine deficiency by measuring the excretion of this neurotransmitter and its metabolites in urine were fraught with difficulty. The proposal that a single metabolite, 3-methoxy-4-hydroxy-phenethylglycol (MHPG, for short), more accurately represented events in the central nervous system provided a new handle. Studies of MHPG excretion in depressions has led to the concept that instead of a simple deficiency of norepinephrine, normal or excessive amounts may be present.[7] Decreased excretion would be consonant with a "noradrenergic deficiency" depression while normal or increased excretion might be construed as indicating a "serotonergic deficiency" depression. The latter idea was supported by measurement of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid. Low levels confirmed the supposition of a serotonergic depression while high levels were assumed to represent noradrenergic depressions, exactly the converse of the situation with MHPG.[8]

Thus, based on knowledge of how drugs act and following the leads provided by this knowledge, at least two different biochemical types of endogenous depression are postulated. If acetylcholine and dopamine are involved, which also seems possible, we may have clinically depressed states involving all of the four major neurotransmitters of the brain, either alone or, more likely, acting in concert.

Clinical Implications

If there are patients with "endogenous" depressions of different types, then it may be possible to delineate the biochemical substrate of their depression and to choose in advance the drug most likely to remedy that abnormality. Thus, we would have both a rational diagnosis, in the sense that it could be confirmed independently of clinical judgment, and a rational treatment, in that the drug would be selected to remedy a specific defect.

It remains to be seen whether or not this hope will be realized. Presently available data provide encouragement, but are by no means conclusive. Nonetheless, we have come a long way from the model of depression induced by reserpine. We are now in a position to postulate hypotheses about the causes of serious emotional disorders and, more importantly, to test these hypotheses. Such an advance is not only the major development in psychiatry of the past 25 years, but of the past 2500 years.

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Food and Drug Administration Regulation of Clinical Psychopharmacology

BURTRUM C. SCHIELE, M.D.*

The Food and Drug Administration (FDA)'s most important consumer protection function sometimes is hindered by political interference or by well meaning amendments to the legislation governing the FDA that are not always workable. The relatively recent "proof of efficacy" requirement may eventually lead to better drugs, but it has had the immediate effect of increasing costs and slowing the development of new agents. Patient package inserts will have a significant impact on future medical practice.

ALMOST DAILY, the Food and Drug Administration (FDA) hits the news. The following comment introducing an article[1] on the current saccharin problem says a lot about why this is so.

> Of all the federal agencies regulating business and consumer affairs, none is more regularly or vehemently denounced than the U.S. Food and Drug Administration. Critics have variously blasted it as arbitrary, ill-organized, arrogant, inbred and inept. There is a reason for the scourging: the FDA affects both consumers and manufacturers where they are most sensitive — in the products that they can buy or sell. The agency regulates everything from lipstick to kidney dialysis machines. All told, the FDA activity touches on 20c of every consumer dollar spent, says an agency public relations man proudly: "The FDA intrudes on your life."

The Food and Drug Administration was created by Congress in 1907: its powers were greatly increased in 1938 when the improper use of Sulfanilamide caused a number of deaths. Over the years, the Agency's responsibilities, its budget and its staff have grown steadily. Today it has approximately 7,000 employees and an annual budget of nearly 300 million dollars.

Problems of the FDA

Partisan Politics

Political interference is the Agency's number one problem as I see it. Unfortunately, politicians have discovered that one way to embarrass the party in power is to start an investigation or to raise a complaint about something the FDA has or has not done. Peter Hutt, the able former General Counsel of the FDA, at a symposium[2] entitled "Who Regulates the Regulator While the Regulator Regulates?" stated:

> In my four years at the Food and Drug Administration, during which I testified before Congress about 80 times, I can recall no oversight hearing that even purported to be a balanced and objective analysis of an issue, and was constructively intended to help the Agency do a better job in the future. They were, instead, uniformly prosecutorial in nature, and designed to embarrass, harass, and intimidate Agency personnel. Their basic purpose was publicity. Most made no attempt to conceal the preconceived conclusions, which were backed up by witnesses and documents carefully culled to present a single viewpoint. Not infrequently, at the end of the hearing the chairman has read a typed summation that was prepared well in advance and prior to listening to any of the testimony. They have been nothing short of staged plays. And the reports that result are one-sided briefs. If any regulatory agency acted that way, it would be reversed summarily and reprimanded severely by the courts. But there is no appeal from a congressional hearing.

The FDA has been the subject of many congressional reviews. The latest such panel was convened after the Senate hearing in August of 1974. The panel's report clears the FDA of charges that it has played "soft" on drug companies. Moreover, the report[3] goes on to say:

> "An impartial reader of the (hearing's) transcript can hardly escape the conclusion that (former FDA Commissioner) Alexander Schmidt and his colleagues had walked into a proceeding the direction of which appeared preordained. They apparently sensed that their reputations would suffer and that exoneration, if it ever came, would not catch up with the accusation. It was unfortunate that they were put in a position like that."
>
> The report labels the publicity surrounding the 1974 hearings "sensational" and notes that the hearings were part of an overall effort in preparation for national health insurance legislation.

The original act has been amended many times by

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Footnote: The opinions expressed in this paper are those of the author and not necessarily those of the Food and Drug Administration.

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Congress. One example is the Delaney amendment which states that any substance which is shown to be carcinogenic in animals cannot be used as a food additive for man. Here, the problem is not so much the intent of the amendment as the wording and interpretation. Unfortunately, the Agency must act before it has an opportunity to study the problem thoroughly. The actions taken on Cyclamates and Saccharin are examples of what can result.

Professional Staff

Investigational reviews of the Food and Drug Administration have been conducted periodically for several decades. A number one recommendation of virtually all of the reviewers has been: upgrade the quantity and quality of the FDA's scientific personnel. Dr. Alexander Schmidt,[4] outgoing Commissioner, agreed heartily.

> The FDA is a highly people-intensive organization, and it is only as good as its staff. If someone wants to create beneficial change in FDA, I think the single most important thing to do is to improve the ability of the Agency to recruit and retain professional staff. FDA is blessed by having on its staff highly competent, hard working, long-suffering professionals, but in totally inadequate numbers for the jobs given the Agency to do. So, give FDA the people it needs, help FDA keep them, or else don't expect so much to be done so fast.

Bureaucracy Syndrome

Doubtless, there is some truth in the often cited criticism that FDA personnel find it safer to do nothing or to say "no" than to take definitive action. The complexity of the organization and its size certainly do not make for speed and efficiency, particularly when the Agency is short on highly skilled professional persons to expedite its work.

Consumer pressures exerted on members of Congress or directly by formal petitions to the FDA increasingly are affecting the FDA's function.

The FDA, however, remains an extremely important agency of great benefit to the American public. Doubters can read the *Efficacy of Self Medication*[5] to get an idea of what the status of medical claims might be like without regulation.

Possible Remedies

Former Commissioner Schmidt,[4] in addition to stressing the need for greater numbers of skilled professionals, believes that the latter should have real research opportunities. If the FDA had its own scientific laboratories, job satisfaction could be greatly increased and the Agency would be better able to attract and retain the persons it needs. In addition, the Agency should be organized in one location instead of being scattered in 23 different sites in the Washington, D.C. area alone.[6]

It has been suggested that the FDA should be greatly scaled down and reorganized along the lines of the British system. The Dunlap Commission (British FDA equivalent) is composed of a relatively small number of highly qualified scientists who make the real decisions at much less expense and with less difficulty than does the FDA.

Proof of Efficacy: A Special Problem

In 1962, with the enactment of the Kefauver-Harris Amendments, the FDA was required to establish efficacy and not just safety before approving a new drug. In the regulations,[7] substantial evidence of efficacy means:

> . . . adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling . . . (Sec. 505(d)).

This amendment necessitated many changes in procedure for evaluating drugs prior to marketing; however, there were no explicit criteria for judging a drug's efficacy. The American College of Neuropsychopharmacology (ACNP), through its Government-Industry Liaison Committee, became interested in this problem in December of 1968. The ACNP has a small membership made up of clinicians (mostly psychiatrists), basic scientists (mostly pharmacologists), and scientific and medical administrators from the pharmaceutical industry and the regulatory and research agencies of the federal government. Because of its interdisciplinary and representative nature, the ACNP was in a unique position to study problems of drug development without being directly involved with the regulatory responsibility or economic motivation. Funded in part by the Psychopharmacology Branch of the National Institute of Mental Health, a task force was set up early in 1969. I was the chairman of the task force. With the help of many collaborators and contributors we produced a series of "white papers" which ultimately resulted in a volume[7] published in January of 1971 entitled *Principles and Problems in Establishing the Efficacy of Psychotropic Drugs*.

In the spring of 1969, FDA Commissioner Charles Edwards ordered "guidelines" for the development of new drugs to be drawn up by the FDA. He asked for assistance from the Pharmaceutical Manufacturers Association. It was hoped that the guidelines would be completed within a few months.

When our task force learned about this FDA project, we expressed the opinion that clinical investigators should be included in drafting the guidelines rather than leaving the job exclusively to the regulatory and manufacturing groups. In time, a number of us were invited to become members of or consultants to the Agency or members of its Psychopharmacologic Agents Advisory Committee.

It is interesting to note that psychiatry, in spite of the vagaries and complexities of the field, appears to be ahead of many other fields of medicine in developing a good FDA-clinical investigator relationship, which is due in large part to the efforts initiated by the ACNP.

Psychopharmacologic Agents Advisory Committee.

One of our first and most important projects with the FDA was to work on the Guidelines for the Development of Psychotropic Drugs in three main classes: the antipsychotic, antidepressant and antianxiety agents. The guidelines were to establish reasonable criteria for how a drug should be developed — how to establish efficacy and safety in the most scientifically reasonable and economical manner. These guidelines included criteria for patient selection (we have much more work to do in this area and perhaps DSM III will help us), the need for control groups who are treated either with a comparison drug or a placebo, the proper application of random or other unbiased assignments of cases, and statistical analysis.

Fears were expressed that the guidelines would be "set in cement" or perhaps would be rigidly and unreasonably applied. So far the guidelines have been subject to reasonable interpretation and have undergone many revisions. They are just now being finalized approximately eight years after they were originally called for, and contain provisions for updating as new advances occur.

Effects of Requirements to Prove Efficacy

The full impact of the 1962 amendments on medical practice may not be known for some years. Establishing efficacy requires a great deal of effort and time, thus the costs are increasing as is the "brain to bottle" lag. These disadvantages may be offset, in time, by improved scientific methods for clinical trials and by greater specificity as to what therapeutic agents do and do not do.

Another effect of the 1962 amendments was the assessment of efficacy for all drugs marketed after 1968. Drugs judged to be effective, of course, were allowed to remain on the market. Those which were judged ineffective were generally removed from the market.

What many physicians do not realize is that a number of the drugs they are still using fell between these classifications; they were judged to be either "probably effective" or "possibly effective." The manufacturer then had eight-10 years to "upgrade" the drug before removal from the market would occur.

For example, phenelzine (Nardil) was judged "possibly effective." The manufacturer sponsored a series of clinical trials which showed it to be efficacious. Thus the drug was updated and will remain commercially available. Tranylcypromine sulfate (Parnate) on the other hand had been rated "probably effective," but its manufacturer did not initiate additional studies. Consequently, it might well be removed from the market unless studies recently begun provide enough evidence of efficacy to allow its upgrading.

Impending Problems

Prolactin and the Neuroleptics

Clinical studies on several investigational antipsychotic medications were suspended because these agents seemed to cause an increased incidence of mammary tumors in rats, presumably related to the increased prolactin secretion induced by these drugs. The issue is of particular importance because virtually all of the currently available antipsychotic medications cause increased prolactin secretion. The FDA and medical science in general are now evaluating this phenomena.

The Patient Package Insert (PPI)

The idea of a pamphlet which tells the patient something about the drug which he is taking is not new. Birth control pills have been accompanied by such patient information pamphlets for some years. Patient information sheets are commonly dispensed with over-the-counter medications.

There is, however, a strong new push in the United States to develop PPIs for certain drugs as soon as possible and for most if not all drugs in time. The FDA was petitioned to do something about this by consumer groups, some of whom appear to be hostile to the medical profession and some of whose demands may be difficult to meet.

Briefly, some of the arguments for the PPI are: (1) the doctor does not have time to explain as much as might be desirable about the drug he prescribes; (2)

even if he does, the patient may forget what the doctor said and should be able to refer back to an instruction sheet in any case; (3) the instruction sheet should tell the patient what troubles (such as adverse reactions) to look for and when to seek help; (4) the PPI allows the patient to take more responsibility for his own treatment and (5) the PPI is thought to be especially helpful in long term treatment and with especially dangerous drugs.

Some of the arguments against the PPI, or at least questions about it are: (1) the government is interfering with the medical practice and the doctor-patient relationship; (2) the patient may become frightened about possible side effects and fail to take the medication (some consumer groups apparently want this to happen as they feel that we are an overmedicated society); (3) who dispenses the patient information circulars — the physician or the pharmacist? (4) how should the PPI be written: at what education level? in how many languages? in what detail? Some people worry about whether psychiatric patients differ from other patients in this regard. There are many legal questions.

Fortunately, those interested in promoting the patient package insert are attempting, and in some cases actually carrying out, studies to evaluate how to write the inserts and what their impact will be. A two-day meeting in November 1976 on the Patient Package Insert was jointly sponsored by the FDA, the Drug Information Association, the American Medical Association, and the Pharmaceutical Manufacturers Association.[8]

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Conference of National Association of Vision Program Consultants

John F. Hick, M.D., Department of Pediatrics, Mayo Clinic, who authored the article, "Comprehensive Pre-School Screening: Right or Ritual?,"* will be the keynote speaker at the Third Annual Conference of the National Association of Vision Program Consultants in Minneapolis, August 5-8, at the Regency Plaza Hotel. Doctor Hick will speak of the conclusions drawn in the article.

The conference is being hosted by the Minnesota Society for the Prevention of Blindness and co-sponsored by Minnesota State Services for the Blind and Visually Handicapped and the Minnesota Department of Health.

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*Minnesota Medicine, May, 1979.

Continuing Medical Education

The scheduled meetings of the Minnesota Urological Society, Inc. for 1979-1980 are as follows:

Pyelogram Conferences:	November 16, 1979 January 18, 1980 February 15, 1980 March 14, 1980	L'hotel de France Minneapolis, MN
Fall Seminar:	September 13-16, 1979 Brainerd, MN	
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Future of Psychopharmacology

NATHAN S. KLINE, M.D.*

The simple answer to the question would be to assume that all factors are going to remain constant, and then simply review ongoing and prospective drug research to deal with psychiatric problems as we now conceptualize and treat them.

This paper takes a path that is considerably more difficult and risky, attempting to predict how we will alter our conception of what constitutes mental illness, and how psychiatric detection, treatment and research will be organized.

Drugs in the future will be used for the detection and classification of mental disease. Biochemical means of detection in advance of actual clinical symptomatology will result in prophylaxis and prevention of mental disease.

Re-evaluation of concepts of treatment, implications of drug induced side effects, societal insight into the chemical treatment of mental disorders, and the pharmaceutical industry's response to drug abuse are some of the areas in the future of psychopharmacology which may bear little resemblance to what we are doing today.

THE ANSWER TO a question is highly dependent upon how it is asked. There is the story of the two students at the seminary quite heavily addicted to smoking. It was mandatory that several hours a day be spent in silent prayer and although there was no specific order issued on the subject the question of whether they could or could not smoke during this period was at best a dubious one. The first student went to Father McMahon, head of the order, and inquired whether it was permissible to smoke while praying. Father McMahon was outraged at even the question which received a vehement negative answer. The other student waited a few weeks and, in the course of a conversation with the same Father McMahon on other subjects, inquired "By the way, Father McMahon, is it permissible to pray while you are smoking?" The good father smiled benignly and said, "Of course, my son. You are indeed a devoted seminarian."

The answer to the question which has been proposed as my subject is going to depend a good deal on how I ask the answer from myself. The simple proposition would be to assume that all other factors are going to remain constant and then to simply review both ongoing and prospective drug research to deal with psychiatric problems as we now conceptualize and treat them.

The alternate path is a considerably more difficult and risky one but in the end may prove more useful. This involves attempting to predict how we will alter our conception of what constitutes mental illness, our decisions on which conditions should and which conditions should not be treated, and how psychiatric detection, treatment, and research will be organized. All of these factors are in a period of rapid shift and it is most unlikely that by the end of this century they will bear too much resemblance to what we are doing today.

Therefore, in order to make predictions about the drugs of the future we have to know:

1. Who is likely to be considered a patient.
2. How the treatment facilities are likely to be organized and
3. How research into drugs is likely to proceed.

Definition of "Patient"

The general in that lovely play "The Waltz of the Toreadors" asked the physician how things are going in medicine. The doctor replies, "We are making great progress, linguistically speaking." There is already a considerable school which has solved the problem of treatment of schizophrenia by declaring it to be a "way of life" rather than a disease. I have engaged in public colloquy with both Drs. Szasz and Laing: I hesitate to say that we even had a discussion much less a controversy or debate since it was virtually impossible to get either one to talk in a rational fashion about the justification for their major premise, i.e., that there really is no such a thing as mental illness. It seems almost a corollary of this point of view that rational discussion itself is irrational and one should respond in terms of "feelings" and "attitudes" rather than by

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Presented at the Symposium on 25 Years of Psychopharmacology, June 4, 1977, Minneapolis, Minnesota.

logic and scientific method. The problem of illegal drug use also could be solved at a stroke by nullifying all laws prohibiting any restrictions on such use; criminal acts such as robbery and even murder could be "solved" by declaring them no longer unlawful.

Although one can point to instances where restrictions on drug use are inequitable and perhaps unnecessary, or to cases where a diagnosis of mental disease is used in a pejorative rather than a diagnostic manner, the fact that there is a twilight time when it is neither really day nor night cannot be used as a basis to conclude that therefore day and night do not exist. There *is* such a thing as mental disease regardless of how one chooses to designate it and I would propose a relatively simple operative definition which I intend to use for the rest of my discussion: "mental illness is an involuntary deviation of thinking, feeling or acting which results in serious pain or limitation of function."

Although I am convinced that the conceptualization of mental illness into the categories we now make use of is likely to be radically revised as we learn more about the biochemical mechanisms involved, I am certain that most of those patients labeled as schizophrenic, affective disorders, and at least some of the neuroses will remain within the proper definition of disease. It also seems to me highly likely that a substantial number of individuals currently labeled as "sociopaths" or "psychopaths" will be shown to suffer from a metabolic disorder which would place their deviant behavior in the "involuntary" category thus making it a psychiatric disorder.

This introductory material in the foregoing discussion clearly suggests the first of the uses of drugs of the future: the detection and designation of various types of mental illness. It may be that drugs will even be unnecessary, i.e., that examination of body fluids such as blood, urine, or saliva will be sufficient. It is my suspicion, however, that the introduction or "challenge" by a chemical agent will produce a response which will clearly designate the type of illness. As I proceed, you will note that I am proposing the use of drugs for purposes other than simply treating already existent pathology. This brings us to the question of how one defines a drug. Probably the best operational definition is that: "a drug is any chemical substance introduced into a living organism which produces a paper."

My conviction that there are biochemical concomitants of mental illness does *not* and, I repeat, does *not*, force one to the conclusion that all mental illness is the result of chemo-pathology. It does mean that the genetic, nutritional, environmental, social and psychological factors which interact with the organism from the time of its conception up to any present moment will result in a measurable chemical deviation in response to certain "diagnostic" drugs. The use of phenylalanine as a challenge for PKU (phenylketonuria) is one example. As already stated, I believe that it will be ultimately shown that most of the psychopaths and sociopaths suffer from a defect of adrenal metabolism which will be detectable likewise by appropriate "drug challenge." Genetic markers in schizophrenia (as suggested by Wyatt) and in the affective disorders (by differences in electrolytes) are examples. Rudimentary work along these lines was done by Kety many years ago showing that certain amino acids cause an exacerbation of schizophrenia and similarly we know that the monamine oxidase inhibitors have the same effect. One of the more interesting investigations we did along this line was a cross-transfusion between an hallucinating schizophrenic patient and a normal control. The one alternative we had not predicted was the one which occurred: the schizophrenic became worse and had much more marked hallucinations. Quite possibly there was some substance in the blood of the normal individual which the schizophrenic "could not handle."

Most certainly there are factors other than chemical ones which in many cases are determinants of whether the psychiatric disorder does or does not become manifest. If we were able to use drugs in order to detect the high risk group, we might be able to much more effectively develop equally specific means of avoiding those factors which would precipitate the pain and social malfunctioning.

As a side comment I would point out that I believe the capabilities of making such determinations already exist but that we are hampered by a rather simplistic model of how to search for such indicators. Biological research in general has leaned all too heavily upon the models of the physical sciences in which the sub-systems are totally inactive or so inert as to be of little consequence. The sub-systems in a biological organism are so intimately inter-related to each other that a change in one almost inevitably leads to not only a change but an effort at compensation in the other sub-systems. Our models of dealing with pharmacodynamics or chemodynamics or for that matter biodynamics necessitate approaches such as compartment models with differential flow rates between the compartments. Even such a model as this is probably too elementary and it is only the use of high speed data processing and the capacities inherent in the third and fourth generation computers which will make it possible to even conceptualize how the problems should be approached.

But the capacity to screen a population for mental illness does not create the reality. At the present time I believe there are only two countries in the world (Israel and the USSR) where annual medical examinations are mandatory. Although we may never reach that same requirement here in the United States, certainly in the course of the next decades regular medical examinations on an annual or semi-annual basis will become very much more common. As the methodology of detection improves, it should be possible to identify long in advance those individuals with potentials for specific psychiatric disorders. Hence DETECTION and CLASSIFICATION of mental disease by biochemical methods is a predictable eventuality.

Techniques for Detection of Mental Illness

With the development of techniques of detection in advance of actual clinical symptomatology the very obvious consequence is PROPHYLAXIS and PREVENTION. At the present time claims for effectiveness in these areas are made almost exclusively on the grounds of wishful thinking. Who honestly knows anything about how to prevent the occurrence of schizophrenia? The very best we can do is suggest that schizophrenics should not marry each other and to recognize that the female relatives of bipolar depressions are more likely to develop the same disorders than individuals from the general population. If we knew the genetic factors involved, it is certainly not beyond the realm of possibility that we could identify specifically those individuals likely to produce offsprings with an unacceptably high potential for occurrence of the disorder. Conceivably there would be nutritional or other biochemical agents that could pharmacologically compensate so that the high risk would be reduced.

In similar fashion the technique of amniocentesis could be extended so that again either by a direct chemical measure or by pharmacological challenge those individuals likely to develop illness could be detected early on in utero and appropriate correction provided or, in cases where this could not be done, the pregnancy could be terminated at an early stage. If one breaks the conventional molds of thinking all sorts of intriguing possibilities exist. Fuller Torrey, for instance, has raised the interesting question of whether schizophrenia may not be a virus disorder. Again some of our own work which was confirmatory of studies in The Netherlands and elsewhere would indicate that there are peaks of birth for schizophrenics in certain months of the year which would be compatible with a theory of virus co-origin. This, of course, immediately suggests the possibility of pharmacological immunization against schizophrenia. These speculations in turn are not incompatible with some of the still questionable evidence that schizophrenia and possibly some of the other psychiatric disorders may be auto-immune reactions which would make them amenable to pharmacoprophylaxis.

At the same level of pharmacoprophylaxis I have already speculated elsewhere about the use of lithium to prevent manic depressive episodes. Certainly not everyone who drinks slightly polluted water develops bacterial infection nor do even a majority of the individuals who drink water without the addition of fluorine necessarily develop dental caries. Nevertheless as public health measures both chlorine and fluorine are now almost routinely added to the water supply. With the accumulating evidence that lithium if properly used is a remarkably safe drug and that its effectiveness in preventing excursions of manic and in most cases severe depressive episodes, one must at least consider the possibility of the addition of this third halogen to the water supply. Let me point out that a substantial number of Europeans drink only bottled waters almost all of which have a substantial lithium content and most of the European spas contain waters with similarly high content of lithium.

As work in this general area expands, it seems to be extremely probable that many of the trace minerals such as copper and magnesium may be indicted as crucial agents in certain of the chelating actions involved in pathological processes including psychiatric ones. Some evidence already exists that this may be true in certain of the processes of "normal" as well as in premature aging. Pharmacological control of these chelating agents could well be crucial.

Bertrand Russell once said, "Most people would rather die than think — and many do." The problem is not quite that simple since it is more often an inability rather than an unwillingness to create the new ways of looking at things which leads us into new areas of therapeutic activity. The whole cycle of birth, infancy, childhood, adolescence, adulthood, aging, senility and death is regarded as "natural" and "normative." If one thinks about the matter instead of merely accepting it, an entirely new perspective emerges. Nature in general continues along the same path unless something interrupts or changes it. Why then does one not remain a child forever? Certain biochemical processes including endocrine ones occur which alter the state of affairs with a whole series of biochemical, physiological, psychological and social consequences. Again the emergence from adolescence to adulthood really does not occur "spontaneously" but as a result of specific enzymatic and other changes. The same holds true with the processes of aging. Let us take something as simple as menopause. It is not a lack of ova which brings about the cessation of this function in women but specific biochemical changes. A short time ago as a newly appointed member of the Scientific Advisory Board at Yerkes Primate Laboratories, I learned almost with a sense of shock that female chimpanzees continue to menstruate and are capable of childbearing up until their death.

If all of these changes in maturation are the result of specific chemical processes, then it certainly is simpler in principle to find the pharmacological agent which will inhibit the change rather than to produce an agent which will bring about a change which would not otherwise occur. I would predict that by focusing on those processes involved in the transformation of one period of life to another that methods of inhibiting or blocking the changes might be found which would allow us to indefinitely delay the ravages of senility. The recent demonstration by Coppen that brain monoamines increase directly with aging may be one of the clues and the use of certain monoamine oxidase inhibitors may actually retard the aging process. There is intense interest despite the skepticism about the claim that a drug of this type already actually does exist. In any case we are already testing some of the claims for this drug and expect to be testing its effect on aging one of these days. There is even some scientific evidence that the life of cells in solution can be prolonged in such a manner. As I have proposed elsewhere if pharmaceuticals can be found to prolong or shorten the various "seven ages" of man, I would urge that consideration be given to the prolongation of childhood as a period of maximum learning capacity and in general a period of substantial enjoyment of existence. By the same token it would be most expedient to get through adolescence in about three hours on some rainy Tuesday afternoon.

Based on the percent of an animal's life that is required for it to reach maturity, man is definitely being short-changed. He really should be living closer to two hundred years. But even if the overall duration is not extended quite that long, at least it would be comforting if there could be reasonable assurance that we would be as vigorous and healthy as possible. Certainly something occurs biochemically in those individuals who live to be centenarians with the full use of all their faculties and with a vigorous enjoyment of life.

Knowledge in this field is probably more advanced than most of us realize and the role of RNA, DNA, cyclic AMP, and a variety of other advances at the level of molecular biology if only appropriately applied conceivably could point the way to pharmacological agents capable of bringing about such modifications. Once again I believe that the failure to accomplish this has been our simplistic view of cause and effect in the biological realm. In a paper on pharmacodynamics I tried to make this point a half dozen years ago but the total audience amounted to no more than sixteen people since a Masters & Johnson type presentation was running my competition. Fortunately today these two presentations are in tandem rather than on top of each other.

Dr. Rosenfeld relates the story of how he struggled to the New York Academy of Medicine one February night through a blinding snow storm where he was to give a paper. It turned out that the audience consisted of one single solitary individual. He figured that if the man was devoted enough to come, he was entitled to hear the talk which was given in full, unabbreviated form. When he was finished he leaned over and thanked the one man audience, asked him if he had any questions, and when he did not, offered to give him a ride home. The audience replied "Just a minute, you can't leave yet because I'm the other speaker on the program."

Once again I believe that the capacity, the chemicals and the means of developing them all exist but remain still in the realm of possibility because of our failure to remodel scientific thinking which easily tends to become conventional and conservative.

Treatment

It's when we reach the area of treatment that consideration must be given to the likely organization of the field of treatment of mental disorders as it will be in the future rather than how it is today. The major role of psychopharmaceuticals in more than hall-emptying the public mental hospitals in the United States is an example of how a chain reaction set up by a few grams of chemical can have widespread social consequences. Without psychopharmaceuticals the planning for patient care in the community could not even be seriously considered. Many of the actions in this area, however, seem to me extremely precipitous and premature. Taking a patient out of a mental hospital and placing him physically back in the community from which he came certainly does *not* secure his reintegration into society. The entire area of returning psychiatric patients to productive participation has been grossly neglected. The American Psychiatric Association does not even have a Committee on Rehabilitation.

Placing a patient on drugs so that his hallucinations and delusions disappear, getting him a job or providing him with welfare money to buy food and clothing does not constitute rehabilitation. Most of the grandiose schemes start off on the asinine premise that the patient is being returned to THE community. The reality of the matter is that THE community is a non-existent chimera. From the initial contact onward, the relationship between the patient and those concerned with his welfare should be directed toward establishing or re-establishing those networks of social and material consequence which are the very essence of successful functioning. Let us concede that we do have pharmaceuticals which are reasonably successful in obliterating symptoms and signs of gross pathology. Remotivation is a much more subtle and difficult task but I do believe that there are "juices" (i.e., pharmaceuticals) capable of enhancing participation in and enjoyment of existence. There are even a few of the presently existing drugs such as the thioxanthines which, in some cases, appear to act in that direction. Incidentally, here again we are caught up by inappropriate models from the physical sciences.

By the conventional methods of testing where it is assumed, for instance, that a schizophrenic is a schizophrenic, we are quite likely to discard a pharmaceutical if it does not act on a "statistically significant" proportion of the total number of cases. Only very recently has there been recognition and the beginning of development of methods to identify sub-groups which may be responsive to a particular kind of treatment even if the mass of patients with the same general diagnosis do not react. Similarly the introduction of Baysian methods to replace the inappropriate Fisherian method has barely begun.

The return of the patient to the community requires that an appropriate network of relationships be identified and provided before the patient is placed. Once again there is probably too much rigidity of thinking as to what would constitute an appropriate model. Certainly for some patients the use of foster homes as traditionally conceived is adequate. For others, jointly shared apartment or communal living is optimal but the abrupt abandonment of psychiatric hospitals is most unimaginative. There are still a substantial number of people (even among those labeled normal) for whom a semi-structured environment is necessary for any sort of peace of mind. Those with a predilection for life in the Armed services, in the rigidities of the academic world or even the bureaucracy of civil service provide nice, near relevant examples. With suitable social planning some of those parts of psychiatric hospitals which now contain empty buildings could be converted into a new type of community which might well meet the needs of former patients. The criterion that a person is not cured unless he can function as an independent entrepreneur, i.e., a self-reliant rat in the rat race, is obviously ridiculous since even most healthy individuals avoid such a role.

There are some practical and uninspiring details having to do with pharmaceuticals which must at least be mentioned. The widespread and dangerous superstition still exists that patients are not really "cured" until they are able to function without medication. This is an archaic hang-over from the days when mental illness was regarded as a form of moral weakness or a punishment for immoral behavior. It is fortunate that the same pathology never developed in respect to diabetes, thyroid deficiency, cardiac arrhythmia and dozens of other physical disorders. Because of this widespread prejudice, psychiatric patients frequently tend to "deny" their illness by discontinuing maintenance medication even though study after study has demonstrated that the rate of relapse is four to five times as great among patients who do not remain on drugs when they are indicated. The relatively recent development of long-acting phenothiazines is almost a necessity if the patient is to be maintained in the community. Now there is not only a once a month injection but an oral form where a single tablet lasts approximately the same length of time.

In addition to the development of similar medications in the antidepressant and antianxiety areas, it is also essential that improved methods be found for detecting whether such patients actually take the medication prescribed. We have proposed one such technique utilizing a radio-opaque band on the once-a-day capsule but certainly this could eventually be improved upon. The hue and cry about our over-medicated society has done much more harm than good since it has little effect on drug abusers but does frighten away from taking necessary medication the very patients for whom it is most essential.

The anti-drug campaigns only encourage the false notion that if you don't take medication that you're not sick. Recently studies by Balter and Levine of the National Institute of Mental Health have confirmed statistically that people are under-medicated rather

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When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

than over-medicated and that roughly half of the population of individuals suffering from "high psychic distress" are not making use of medications which would provide substantial relief. In addition to long-acting medications, it requires no great mantic insight to recognize that more rapidly acting antidepressant medications must be forthcoming. Perhaps the TRH (thyroid releasing hormone) so recently described by Prange is the first of such a group.

The most exciting prospect of all is the possibility of administering pharmaceuticals at the appropriate site of action in a specific area of the brain or other appropriate organ. At the present time in order to have a few picograms of a substance reach an area of a few millimeters, we dump a relatively vast quantity into the gullet or inject it into the blood stream where 99% of it is not only wasted but may be productive of side-effects. Ambrose Bierce defines a medicine as "a stone flung down Broadway to hit a dog on the Bowery." We ourselves are involved with the work of Delgado in developing chemotrodes which will permit such a specific application of a drug at the specific site of action. Incidentally the same technique can be used to identify the chemopathology making it possible to settle rapidly and convincingly most of the current controversies about mode of action. Measuring the content of the sewerage coming out of a hotel, the composition and quantity of water being used and the overall number of kilowats consumed is really not all that helpful in discovering what is going on in Room 2314.

This, of course, does not mean that side effects should be neglected since it is an aphorism that "today's side-effects are tomorrow's therapy." Adverse reactions should be regarded not purely as nuisances to be disposed of but should be studied to determine whether the effect produced has therapeutic application in some other medical disorder. There are several other theme songs which I almost hesitate to mention since I have been harping on them so long, i.e., that the general practitioner should be the first line of attack in handling psychiatric disorders and certainly should be the physician responsible in almost every case for the long term maintenance of patients. This would avert the stigma which unfortunately still exists that patients have about going to aftercare clinics or psychiatric facilities.

We have even moved beyond the pure "physician" stage today and there is no question but that paramedical personnel can be adequately trained to supervise and even prescribe medication in a very substantial number of cases. This has been amply demonstrated by such pioneers as Lambo in Nigeria. In our own private practice in Manhattan, the nurses do precisely the same thing within very specific limits. As with all medical practice one of the most important factors is to know the limits of your capacities and as long as this caveat is followed psychopharmaceutical care could be much more readily and inexpensively available. The capacity of the general public is also vastly under-rated and I truly believe that within a decade intelligent use of self-medication, i.e., over-the-counter drugs could and should be made available for a variety of the more simply treated psychiatric disorders.

In all of these areas much more effective methods must be developed and more time devoted to evaluating the efficacy of both the treatment and the delivery system to determine both how to make the appropriate drug available and how to determine whether it is being used.

In addition to attempting to eliminate side-effects — and we now have the first potent antipsychotic agent which does not produce extrapyramidal symptoms — some thought should be given to producing drugs which *do* have side-effects. In most of the Orient opium is not such a dangerous drug since it is eaten and when consumed orally in large quantities it produces nausea. Perhaps similar side effects should be actually built into medications so that overdoses would produce vomiting and reduce the danger of fatality. Inducing unpleasant side-effects might also produce enough adverse conditioning to prevent the development of habituation or dependence.

I will touch only briefly on the subject of drug abuse since I believe that there is a legitimate need for pharmacological relief from psychic and emotional stress. This need varies from one individual to another and it may well be that in certain individuals the requirement is extremely high.

In such cases the pharmaceutical industry could certainly produce a superior substitute for alcohol, heroin, and tobacco were the need for these agents recognized as a legitimate medical necessity. Instead of attempting to find methods to prevent the abuse of these agents, that is, alcohol, opiates and tobacco, a major effort should be undertaken to find safer substitutes since they obviously serve an extremely useful purpose which we have no other means of satisfying at the present time. This focus on prevention seems to me largely misdirected and I will predict that in the course of the next decade it will be recognized that the major focus should be on the development of safe and effective substitutes.

There are one or two other slightly unconventional thoughts which I have occasionally put into operation. At times the psychiatric difficulties of patients are precipitated or accentuated by relatives who may themselves fall within the borderlines of "normality." On one or two occasions I have been able to convince such "normal" husbands or wives or parents to take medications which will reduce their anxiety or guilt to a point that they will stop annoying and provoking my patients. I recall a play in which the wise old pediatrician was called to see the sleepless hyperirritable child and then proceeded to write out a prescription for a sedative to be given to the *parents* so that they would stop disturbing the child long enough to let it rest. It might be useful for nurses, attendants and even psychiatrists who have to deal with disturbed patients to be appropriately medicated if their own reaction patterns are such that they would otherwise be counterproductive in terms of good therapy for the patient. I am reminded of a favorite patient of mine who, in speaking of one of our most prominent television producers, said "Fred isn't neurotic himself — but, boy, is he a carrier."

Finally let me point out that there is no basic conflict between pharmacotherapy and other techniques of treating and improving the lives of psychiatric patients. In fact, to a substantial degree, the various types of psychiatric treatment supplement and complement one another. There are some cases in which pharmacotherapy is unquestionably the major modality of treatment but there are other instances where drugs are useless or even detrimental. The same, of course, is true of other types of treatment. Insights may be raisins in the rice pudding of psychotherapy but, as a rule, we require a more substantial well-balanced diet of which pharmacotherapy is already an essential ingredient.

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Hennepin County Medical Center, Minneapolis
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September, 1979

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September 6-8, 1979 — Minneapolis Auditorium
Fee: $350 Credit Hours: 14, Category 1

The meeting, will concentrate on what can be done to help the hearing impaired from a medical, surgical, audiological and rehabilitative standpoint.

Reproductive Biology, Sexual Dysfunction and Gender Dysphoria (Leadbetter Symposium) — September 6-8, 1979
West Bank Auditorium, University of Minnesota, Minneapolis
Fee: $350 Credit Hours: Estimated 23, Category 1

Symposium will cover the topics of male impotence, premature ejaculation, endocrine dysfunction, Peyronie's disease, infertility and transexualism.

Chest Radiology (42nd Annual Course) — September 10-14, 1979
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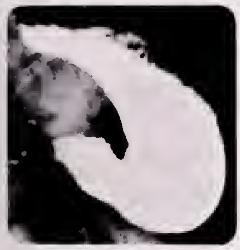
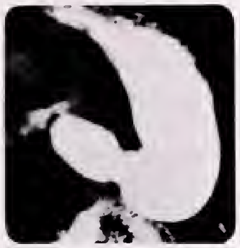


Pylorospasm has almost totally blocked passage of barium meal.



Barium meal beginning to pass 10 minutes after intramuscular injection of 20 mg. Bentyl.

"The correlation of spasm relief and drug given was excellent."

---

*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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INDICATIONS
Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as "probably" effective:

For the treatment of functional bowel/irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

THESE FUNCTIONAL DISORDERS ARE OFTEN RELIEVED BY VARYING COMBINATIONS OF SEDATIVE, REASSURANCE, PHYSICIAN INTEREST, AMELIORATION OF ENVIRONMENTAL FACTORS.

For use in the treatment of infant colic (syrup).

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea, vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION Dosage must be adjusted to individual patient's needs.

Usual Dosage Bentyl 10 mg capsule and syrup: *Adults*: 1 or 2 capsules or teaspoonfuls syrup three or four times daily. *Children*. 1 capsule or teaspoonful syrup three or four times daily. *Infants*: ½ teaspoonful syrup three or four times daily. (May be diluted with equal volume of water.) Bentyl 20 mg.: *Adults*. 1 tablet three or four times daily. Bentyl Injection: *Adults*. 2 ml. (20 mg.) every four to six hours intramuscularly only. NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE: The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

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Letter to the Editor

Dear Editors:

Health Care Cost Commission

I have just received in the mail the policy statement of the Minnesota Medical Association based on the action of the House of Delegates at its annual meeting. I feel it would be useful to include with the item by item summary of the recommendations on the report of the Commission on Health Care Costs a description of the various categories of action; particularly I think it would be important to emphasize the difference between Approval in Principle and Full Approval, since there was considerable debate and some disagreement on items which received the Approval in Principle action as opposed to Full Approval.

Thank you very much for your consideration of this matter.

Brian Anderson, M.D.
Anoka, Minnesota

Dr. Anderson:

The actions of the House of Delegates in response to the recommendations of the Minnesota Commission on Health Care Costs appeared in the July issue of MINNESOTA MEDICINE, pages 555-559.

The MMA House of Delegates gave six basic responses to the report of the Minnesota Commission on Health Care Costs. They were:

A. Full Approval,
B. Approval in Principle,
C. Referral to the Board of Trustees for further study,
D. Referral to the Board of Trustees for reconsideration of existing MMA policy,
E. Reaffirmation of existing MMA policy
F. Not Support

Delegates defined the difference between A and B as one of level of support. Full Approval is defined as active support as well as agreement with the entire recommendation. Approval in Principle, on the other hand, is limited to agreement with the basic, conceptual sense of the recommendation; it implies some reservation about some aspects of the recommendation and/or its implementation.

The Editors

MINNESOTA MEDICINE

The Board of Editors of MINNESOTA MEDICINE invites the members of the Minnesota Medical Association to submit examples of their art work for publication on the cover of MINNESOTA MEDICINE. Color photographs, preferably transparencies, as well as photographs of paintings, drawings, sculpture, ceramics, jewelry, etc., are all welcome. There is no limit as to subject, but pictures of Minnesota or subjects topical to a month or season may have a slight advantage. Pictures will be returned if identified with the name and address of the maker. Please submit pictures to the Editor of MINNESOTA MEDICINE, 101 East 5th St., Suite 900, St. Paul, Minnnesota 55101.

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Rheumatology Corner

Salicylates

RICHARD B. TOMPKINS, M.D.*

A CRUDE EXTRACT of willow bark was used as herbal medicine in the treatment of rheumatism and arthritis. Initially, it was not known what the active ingredient of the extract was, but eventually salicylic acid was discovered in the preparation, and this led to the development of acetylsalicylic acid, the first and still the most widely used of the nonsteroidal anti-inflammatory, antipyretic, and analgesic preparations in the treatment of the rheumatic diseases. Over the last 15-20 years, a variety of other nonsteroidal anti-inflammatory agents have been developed by the pharmaceutical industry, but none has supplanted acetylsalicylic acid as the drug of choice for the chronic therapy of most of the rheumatic conditions.

Of the salicylates, acetylsalicylic acid is the most widely used preparation. It is an active ingredient in many over-the-counter anti-arthritic, analgesic, and cold preparations. The amount of acetylsalicylic acid present in these preparations varies considerably. Therefore, it is preferable to use 5-grain acetylsalicylic acid preparations, so that both the patient and physician know how much of the active drug the patient is receiving. There is no good evidence to document that one aspirin preparation is more efficacious than another in the treatment of the rheumatic diseases, and patients should be encouraged to buy the least expensive preparation they can find. If this preparation is not well tolerated in the upper gastrointestinal tract, one of the buffered preparations can be used. In patients who are truly allergic to acetylsalicylic acid with nasal polyps and asthma, sodium salicylate is almost always tolerated without reaction. There are several 10-grain salicylate preparations with slow release over approximately eight hours which can be used at bedtime to avoid patient awakening for a nighttime dose.

Aspirin is taken in divided doses throughout the day, usually at least four times a day. Most average size adults can take approximately 60 grains of aspirin a day without untoward side effects. As people become older, their auditory apparatus becomes more sensitive to salicylates and tinnitus or decreased hearing may occur at doses less than the optimal ones. In these instances, the dose should be regulated by the appearance of the tinnitus or decreased hearing. In general, a blood salicylate level of 20 mg percent is desirable in the treatment of the inflammatory rheumatic diseases such as rheumatoid arthritis. In rheumatic fever, levels in the range of 25-30 mg percent may be needed but these patients need to be monitored carefully when salicylates are pushed to that extent.

The most disturbing side effect of the salicylates is irritation of the upper gastrointestinal tract mucosa. Salicylates can cause gastric erosion and ulceration. In the vast majority of patients who are treated with salicylates for rheumatic diseases, this is not a major problem. However, if upper gastrointestinal tract intolerance is a problem, one can try enteric-coated preparations, buffered preparations, or choline salicylate. If these are not tolerated or are not helpful, one of the other nonsteroidal anti-inflammatory medications can be tried, although these can also irritate the upper gastrointestinal tract. Salicylates cause platelets to lose adhesiveness, an effect which lasts throughout the life span of the platelet. This is the basis for its use in patients with vascular diseases. Salicylates can cause elevation of the serum glutamic-oxalocetic transaminase, an effect which is reversed by either lowering or stopping the medication.

In summary, salicylates are the drug of choice in the treatment of most of the rheumatic diseases, especially the inflammatory arthritides. They are generally well tolerated, and none of the newer nonsteroidal anti-inflammatory drugs have been shown to be more efficacious than acetylsalicylic acid.

---

*Assistant Professor, Mayo Medical School, Rochester.

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Physicians, Pharmacists and Refills

Lowell J. Anderson, R.Ph.,
Past President and Chairman of the Board of Directors, Minnesota State Pharmaceutical Association

IN THIS PERIOD of increasing costs in our practices and increased political scrutiny of those costs, it is a good time for physicians and pharmacists to take a critical look at the prescription refill process in Minnesota. And maybe find a way that it can be made more cost effective.

The original reason for the state requiring a pharmacist to obtain a refill authorization from the prescriber, and for the prescriber to act on that request, was so that the physician could retain control of the drug regimen of the patient. A good idea. But several decades ago when the Federal Drug Law was passed, it did not anticipate the patient load of 1979 nor its attendant paperwork and expense. The same system clearly does not work in 1979, and as a result both physicians and pharmacists are being placed far out on the liability limb.

In my pharmacy practice 70% of new prescriptions have no indication as to the wishes of the physician in the matter of refills, and therefore are not refillable. This 70% includes such maintenance drugs for which refills are the usual, rather than the exception. Our expense is increased, the physician's expense is increased, and the patient waits. And sometimes does not return to either the physician or the pharmacist.

When pharmacists call for refill authorization, in only 10% of the calls do we speak to the physician. The remainder of the time we speak to someone unknown. It may be a person authorized to transmit information or even authorize the refill — or it may be the janitor! We don't know. The chart may or may not be noted that a refill was authorized. We don't know. We are both out on a limb. One can only wonder as to the ability of the receptionist to make judgment as to the continuation of a particular drug when the two leading questions are: "How do you spell the patient's name?" and "How do you spell the name of the drug?" Followed by "Yes, that's okay to refill."

The average time spent on the phone by a pharmacist waiting for refill authorization is 40 seconds. One call does not represent alot of time. But when multiplied by 200, 100 or even 50 during a typical pharmacy day, it does amount to a lot of time and expense. In one sample, 20% of calls were not returned 'til the following day — one not even returned at all! That results in short tempers all around. From the physician's side that amount of phone work in some offices must require a substantial amount of personnel time just to process the calls. That type of expense is difficult to justify, especially when it is unnecessary.

A number of physicians now include a statement on their prescription blanks to the effect "Don't call us after hours or on weekends for refills." After hour calls are as distasteful for the pharmacist as they are for the physician, yet there are times when that call must be made. What happens when the answering service has been instructed not to transfer pharmacy calls? Do we as pharmacists refill the prescription illegally? Or, does the patient do without the drug? If we refill it illegally, in the eyes of the law it is the same as selling it on the street corner. Our license to practice is in jeopardy. If we tell the patient to wait 'til the physician's office opens, we may have disrupted the prescribed drug regimen.

How about the pharmacist dispensing enough to last 'til the prescriber can be reached? A workable idea, and one which on occasion should be used, even though the law does not provide for its use. But it is for use in unusual cases — not for routine use. If the exception becomes routine, it only points out the fallacy of the system.

There is presently a "game" being played by some Twin Cities physicians when a patient calls them on an evening or weekend via the answering service for a prescription. The patient calls the answering service. The answering service calls the physician. The physician calls the patient. The physician tells the patient to have the pharmacist call for a prescription. The patient calls the pharmacist. The pharmacist calls the answering service. The answering service calls the physician. The physician calls the pharmacist. The pharmacist calls the patient. A total of *eight* calls! Had the physician called the pharmacist directly after speaking with the patient, only *four* calls would have been needed. Everyone would have saved time.

So how do physicians and pharmacists work together to make the process work more efficiently? Most obviously, we must each understand the elements of the others' practices as they interface upon our own.

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Index to Advertisers

American Medical Association 572

Anderson, C. F. Co. 586

Army Reserve 616

Beltone Electronics Corp. 614

Burroughs-Wellcome Co. 604

Carousel Porsch-Audi 568

Classified Advertising 620

Finley & Friday, Inc. 566

Lilly, Eli & Co. 592

Mead Johnson Pharmaceutical Division 597,598

Medcalf Orthopedic Appliance Co. 591

Medical Protective Company 612

Merrell-National, Inc. 586, 587, 608, 609, 610

Merck Sharp Dohme 572

Metro Surgical Supplies Inc. 612

Minnesota Medical Association 622

Pharmaceutical Manufacturers Association 618, 619

Roche Laboratories .... Cover 2, Cover 3, 4

Smith, Kline & French 607

Trautmans 610

United States Air Force 526

Upjohn Company 588

There should be an understanding of the drug laws that constrain the actions of pharmacists; that if the physician's prescription is silent as to refills, it is the same as saying there are to be no refills. That Schedule II prescriptions must be signed and received by the pharmacist within 72 hours, after which time the pharmacist assumes liability unless the physician's neglect is reported to DEA. That some prescriptions cannot be refilled. That some drugs have federally imposed limitations on the number of refills which cannot be over-ruled by the physician. And other issues that can be discussed between individual pharmacists and physicians.

The legal restrictions imposed upon each profession by the drug laws should be a required course in each college. Presently, the subject is not addressed at all in medical school.

One of the services that pharmacists perform for the patient and the patient's physician is the monitoring of patient compliance in the area of drug use. To assist pharmacists in doing this, some 80% of the state's pharmacies voluntarily keep medication profiles of our patients. These records are open to use by physicians, but only in rare instances are they used by the physician.

To further assist us in those efforts, we need to know what the directions for use of the drug are to be. Even though most physicians now include specific directions on new prescriptions, many times they are changed without the knowledge of the pharmacist. This results in our not knowing whether a change in rate of consumption of a drug is as the result of the precriber's directions or something the patient read in "Readers Digest." If the physician at the time of changing a prescription's directions would make a note or call to the pharmacist so that we can change the sig., we could do a better job in this area. We cannot make these changes upon the advice of the patient.

Many times the physician tells the patient to have a prescription refilled which is not refillable. It is then difficult for the patient to understand when a pharmacist says that it cannot be refilled. A call or a note from the physician to the pharmacist would solve this problem also.

The physician and the pharmacist should together establish a protocol for refills. This could be by therapeutic classification: antibiotics can be refilled for a total of 10 or 15 consecutive days unless otherwise noted, antihistamines for six months or a year, maintenance drugs for one year, and so on. This type of understanding would lighten the refill load for both of us; and at considerable savings to both professions.

The subject needs more discussion and understanding. I hope that both of our associations pursue it as well as each of us as individual practitioners within our community.

Annual Autumn Seminar
Obstetrics and Gynecology
October 24-26, 1979

The Department of Obstetrics and Gynecology of the University of Minnesota Medical School, under the direction of Dr. Leon Adcock, will present the annual Autumn Seminar on Obstetrics and Gynecology on October 24-26, 1979, at the IDS Center Conference Theatre in Downtown Minneapolis.

The seminar is designed for all physicians who provide obstetrical and gynecologic care, but particularly obstetricians, gynecologists, family physicians, and internists.

On behalf of the membership, the President welcomes the following into the Minnesota Medical Association with all its attendant privileges, benefits, and responsibilities: Joel W. Arney*, Mark W. Gray, M.D., Tamara L. Hudrlik*, Peter C. Janes,* Peter A. Jernigan, M.D., Merton A. Johnson, M.D., Thomas A. Jones,* Steven P. Kulenkamp, M.D., Thomas R. Martin, M.D., Karl R. K. Nicholes, M.D., Joseph C. Opie,* Gary L. Paulson,* Michael J. Saunders,* Mark M. Segall, M.D., Sylvia M. Sekhon, M.D., Dennis L. Shubert, M.D. and Deborah L. Wexler.*

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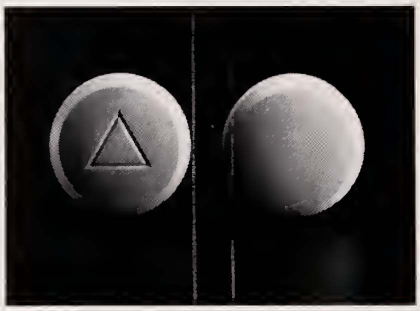
The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

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FAMILY PRACTICE opportunities in outstanding Southern Minnesota Group. The Albert Lea Clinic, P. A., is interested in contacting physician candidates for city and small town branch practices. This group is a 16 man multispecialty group in the primary and secondary care fields. Top salary first year. Senior physician participation beginning at the end of the first year, in incentive income distribution plan. Low cost buy in. Maximum profit sharing plan. Top level insurance plan and full range of other benefits. New hospital in city. Albert Lea is an exceptional place to live and these are choice practices. Please contact B. J. Boss, Administrator, Albert Lea Clinic, P. A., 1602 Fountain St., Albert Lea, MN 56007, Phone 507-373 8251, personal phone 507-377 1406 or contact Gary Boeke, M.D., 507-373 8251, personal phone 507-826-3288.

FAMILY PRACTITIONERS needed immediately to join present four physician corporate group practice in rural Southwestern Minnesota; guaranteed income with liberal fringe benefits; full partnership after one year; no investment necessary; new clinic facility attached to newly renovated hospital; area offers excellent recreational activities; top school systems; warm community atmosphere. Contact J. L. Bader, M.D., Chief of Staff, Slayton Clinic, 2042 Juniper Avenue, Slayton, MN 56172; Phone number: (507) 836-6153 or 836-6463.

WANTED: GP to join two GP's in practice in rural community northern Minn. Mod. clinic bldg. with good xray & lab facilities. 40 bed hosp; 100 bed nursing home. Also need locum tenans for summer vacations. Contact W. A. Pinsonneault, MD, Warren Clinic, box 107, Warren, MN 56762 (218) 745-4151.

APPLICATIONS WELCOMED from board-qualified or certified radiologists. Large teaching hospital, upper midwest; University affiliation. Subspecialty training in nuclear medicine desirable. Box 529, Minnesota Medicine, 101 E. 5th St., St. Paul 55101.

THE FARIBAULT CLINIC, LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

PRACTICE WHERE there is an abundance of clean air and outdoor activities — in the heart of Minnesota's lakes and woods. Excellent opportunity for 1 F.P. to join with 6 F.P's., 2 General Surgeons and 2 Physician Assistants. New clinic building. 50 bed hospital with 5 bed ICU-CCU. Contact William Pauley, Park Rapids-Walker Clinics, LTD., 120 N. Main, Park Rapids, MN 56470. Phone 218/732-3325.

OPHTHALMOLOGIST WANTED IN SOUTHERN MINNESOTA Group Practice. The Albert Lea Clinic, P.A., in Albert Lea, Minnesota, a 16 man multi-specialty group is seeking a replacement for a senior man. Board certified or Board eligible. Salary guaranteed first year. Second year, participant in clinic's incentive income distribution plan. Low cost buy-in arrangement. Profit sharing plan. Top insurance plan with full range of other benefits. New hospital in city. A choice practice and exceptional place to live. Contact William Brouwer, Assistant Administrator, Albert Lea Clinic, P.A., 1602 Fountain Street, Albert Lea, Minnesota 56007, phone 507-373-8251, personal phone 507-889-6381 or contact Gary A. Boeke, M.D., 507-373-8251, personal phone 507-826-3288.

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GENERAL SURGEON or internist needed to take over 27 year practice by May-July, 1980, in two college city. 42 miles from Twin Cities. Write: MINNESOTA MEDICINE — 543 — 101 E. 5th St. #900, St. Paul 55101.

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WANTED— M.D. or D.O./FAMILY PRACTICE to join gr. of 3 FP/MD's. Exc. new clinic attached to 120 bed hosp. Full hosp. priv. avail. Salary 1st yr. then may join corp. Thriving comm. of 10,000 + with lg. drawing area. Fine recreational and social area with first class school system & all churches avail. Easy freeway access to metro area. Contact Family Clinic, 808 3rd St. S.E., Little Falls, MN 56345 or call collect D. R. Seifert M.D. (days) 1-612-632-2301, (evenings) 1-612-632-9150.

MEDICAL BUILDINGS: We offer specialized Planning, Financing, and Construction services for group practice facilities and medical office buildings. Contact James Verhey, NORMANDALE ASSOCIATES, INC. 4813 Hibiscus Ave. Minnneapolis, Minnesota, 55435. (612) 925-3101.

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PHYSICIANS — Metropolitan Medical Placement offers assistance through our no obligation to the physician placement service. We always have several active listings throughout Minnesota and we specialize in *aggressively* seeking our opportunities to match each physician's individual needs. If you desire confidentiality and professionalism in our search efforts, then we ask you please to contact Mr. Holmes at 612-831-5232.

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FAMILY PRACTITIONER, OB-GYN, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

INTERNIST AND FAMILY PHYSICIANS wanted by 10 person medical group in Alexandria, Minnesota. Please contact Paul H. Engebretson, M.D., 610 Fillmore, Alexandria, MN 56308. Telephone: (AC612) 763-5123"

(Continued from page 623)

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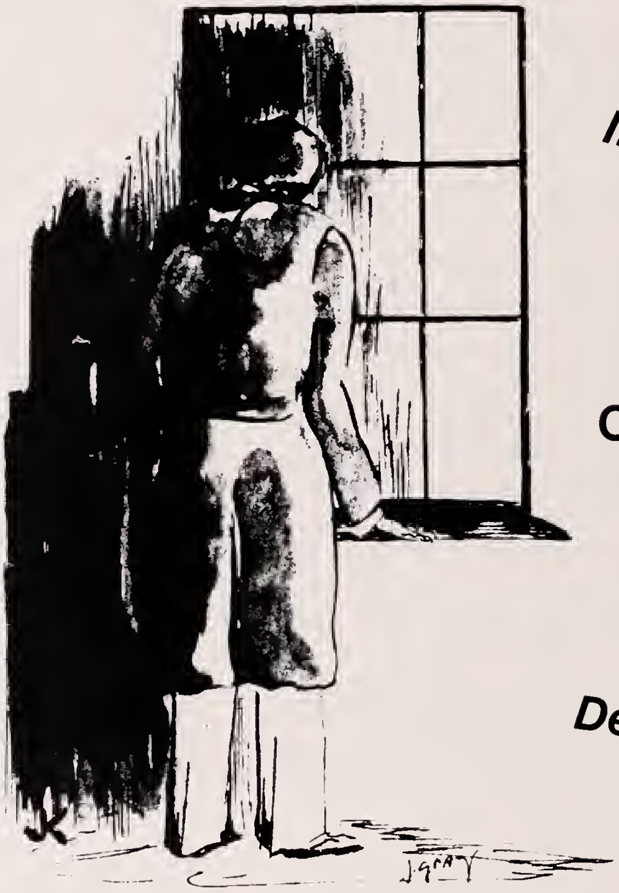
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(Continued from page 621)

Internist and family Practitioner wanted for congenial democratic seven man group; one General Surgeon, one OB/GYN and five Family Practitioners. Salary in the $40,000 to $50,000 range depending on qualifications; full buy-in privileges and equal partnership after one year of practice. For more information contact JM Doty, MD, FACOG, Medical Center, Little Falls, Mn. 1-612-632-6611.

Internist: Certified or Board Eligible to join the staff of this 409 bed, University affiliated VA Medical Center located in the Black Hills of South Dakota. Position offers both clinical and academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. This area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD 57741. Phone 347-2511, Ext. 497. Equal Opportunity Employer.

Psychiatrist — Board Eligible or Certified to take charge of a 30-bed ward in this 409 bed, University affiliated VA Medical Center located in the Black Hills. Position offers clinical, and possible academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. Area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD. 57741. Phone (605) 347-2511, Ext. 497. Equal Opportunity Employer.

Experienced general surgeon needed to join two general internists, a gastroenterologist, four family practitioners and a pediatrician in a busy Satellite of the Marshfield Clinic at Ladysmith, Wisconsin. Complete details and personnel interview will be arranged for qualified applicants. Send curriculum vitae, bibliography and three references to William M. Toyama, M.D., Department of Surgery, Marshfield Clinic, 1000 N. Oak Avenue, Marshfield, Wisconsin 54449.

Family physician to join expanding group of family physicians. Downtown Minneapolis location adjacent to Metropolitan Medical Center. Contact Donald Blowers, M.D., or Roxanne Butler, Business Manager, Parkside Family Physicians, P.A., 825 South 8th St., Mpls., Mn. 55404. Phone 375-1700.

Family practitioner wanted. 25 doctor multi-specialty group in scenic Hiawatha Valley needs Family Practitioner to staff a branch office 18 miles from the main clinic. Doctor may opt to live in Winona or the rural community. Diversified recreation. Excellent public and parochial school systems, including three four-year colleges. The Clinic currently is successfully staffing one branch office, and is committed to staff a second. Must be Board certified or Board eligible. Salary guaranteed. Liberal fringe benefits, including pension plan and profit sharing plan. Incentive system after one year. For additional information, write or call Dr. Andrew E. Edin, Chairman, Recruiting Committee, Winona Clinic, Ltd., 420 E. Sarnia Street, Winona, MN 55987. (507) 454-3680.

"Wanted" — Internist or Family Practitioner as Full-Time medical consultant on Chemical Dependency Unit from January 1 to July 1, 1980. Contact: Richard M. Shick, M.D., Chairman of Department of Medicine, Rochester State Hospital, Rochester, MN 55901. Phone (507) 285-7002

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(Continued to page 624)

(*Continued from Page 623*)

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TWO INTERNISTS — Wanted to join an 11 physician multi-specialty group. Hospital equipped for colonoscopy and gastroscopy. Located in a progressive city of 13,000 with excellent schools and recreational area around a chain of 5 lakes. If interested, call or write: Don Grandgenett, Administrator; Fairmont Medical Clinic P.A., 800 Clinic Circle, Fairmont, MN (507) 238-4263.

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POSITION AVAILABLE — READVERTISED — South Dakota State University's search for a Student Health Staff Physician is still in progress. HEALTH SERVICE PHYSICIAN—GP, FP, or INTERNIST to share out-patient care and treatment for 6000+ students on the attractive Midwest campus of South Dakota State University. Exceptional staff and facilities for student care. Excellent hours. Free weekends. Flexible contract: 9-12 months. Must be interested in providing general primary medical care for college age pop. Very competitive salary with excellent fringe benefits. Some experience in adolescent or college practice is beneficial but not required. Position open immediately. Send resume and 2 references or call collect James O. Pedersen, Dean of Student Services, (605) 688-4121, South Dakota State University, Brookings, S.D. 57007. The University is an Affirmative Action/Equal Opportunity Employer (Female/Male).

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. Oral—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

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Contents — September, 1979

COVER PHOTOGRAPH — "Autumn in Wisconsin"
Richard N. Hadley, M.D. 662

PRESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association 629

EDITOR'S NOTEBOOK
Richard L. Reece, M.D.
Editor-in-Chief 631

ORIGINAL CONTRIBUTIONS

Health Care Problems among the Southeast Asian Refugees — "The Boat People"
Neal R. Holtan, M.D. 633

Septicemia and Pleural Effusion from Eikenella Corrodens — A Normal Mouth Inhabitant
Paul Stiegler, M.D. 635

Atopic Dermatitis Associated with Citric and Malic Acid Intolerance
William E. Walsh, M.D. 637

The "Square Knot" That Slips
John Strickler and Paul Gannon, M.D. 643

Figure Skater's Foot
Michael W. Davis, M.D. and Thomas Litman, M.D. 647

Achalasia of the Ureter
Michael Bjork, M.D. 649

Scintiangiographic Identification of Lesion Producting Foix-Alajouanine Syndrome
Clarence E. Henke, M.D. et al. 653

Diagnosis of Acute Knee Injuries
James D. Priest, M.D. 657

CASE REPORT — Tracheal Cylindroma — Report of a Case with External Tracheal Prosthesis
Richard C. Woellner, M.D. and Alan C. Hymes, M.D. 660

LETTERS TO THE EDITOR

Senior Citizen Retired Physician
J. C. Cain, M.D. 667

U.S. Health Care System
William J. Klein, Jr. M.D. 668

Uremic Pericarditis —
T. J. Buselmeier, M.D. 669

PATHOLOGIC ANATOMY — Testicular Surprises in Two Apparently Healthy Young Men
Miles J. Jones, M.D. and Gene P. Siegal, M.D. 671

SPECIAL ARTICLE — Lung Cancer Patients Treated with Corynebacterium Parvum —Phase I Toxicity Study
Richard YaDeau, M.D. et al. 673

RHEUMATOLOGY CORNER — Nonsteroidal Anti-Inflammatory Drugs
Richard E. Tompkins, M.D. 677

MINNESOTA DEPARTMENT OF HEALTH — Viral Hepatitis in Hospital Personnel in Minnesota — Report of a Statewide Survey
Michael Osterholm, M.D. and John S. Andrews, Jr., M.D. 683

CONTINUING MEDICAL EDUCATION 632, 636, 639, 655, 675, 678

CLASSIFIED ADVERTISEMENTS 691

INDEX TO ADVERTISERS 690

Volume 62:9
Pages 625-694

MINNESOTA MEDICINE REPRESENTS

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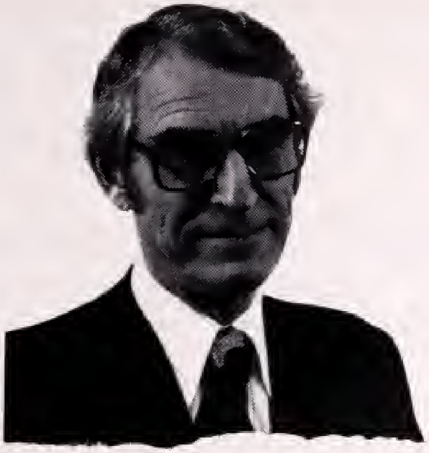

President's Letter

Accompanying the Journal this month is a physician's roster which is current and complete based upon information supplied by the component medical societies. Every effort has been made to avoid the omission of names of practicing physicians and to eliminate inaccuracies. Members should be aware, however, that the reliability and consequent value of this roster is directly related to the accuracy and completeness of the information which our MMA staff receives from the component societies. If, therefore, anyone feels that the listing for his local society is deficient we would appreciate his taking action at the local level to correct that deficiency and thus avoid its repetition the next time the roster is published.

At the state level we will continue to seek ways to improve data collection, retrieval and analysis in order to better serve the membership. It is our hope that the roster in its present form will obviate the need for component societies to publish a local roster. Suggestions for improving the content and format of the roster are welcome and should be directed to Mr. Don Linder at the MMA office.

We are all aware that the cost of publishing a quality journal such as Minnesota Medicine has risen sharply. A desire to maintain quality and avoid an inordinate drain on dues dollars presented a challenge which fortunately the Journal's editorial board and finance committee accepted. They have responded with several innovative and cost saving measures. Important among the changes instituted was discontinuing publication of the physician's roster which until this year was a budget item of Minnesota Medicine.

This year the roster was printed for us by Minnesota Blue Cross — Blue Shield. Mr. James Regnier, president of that organization, has established a reputation for being sensitive and receptive to any change which may serve to improve communication with and between physicians. He was quick to recognize that printing of a first class roster was a legitimate way for his company to provide a needed public service. We wish to thank the Blue Cross-Blue Shield Corporation for helping us in this way and to congratulate the editorial board of our Journal for their continuing effort to upgrade quality and reduce cost.

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

The Minnesota Medical Association,
its officers, trustees,
delegates and members,
extend its sincere thanks
to
Minnesota Blue Cross-Blue Shield
for the printing of the
excellent roster
mailed with this issue
of
Minnesota Medicine

See President's Letter, page 629.

Editor's Notebook

All Things Considered

"The time has come," the Walrus said,
"To talk of many things:
Of shoes – and ships – and sealing – wax –
Of cabbages – and kings –
And why the sea is boiling hot –
And whether pigs have wings."

Lewis Carrol
"Through the Looking Glass"

The Authors Have Their Say

"The time has come," this issue's authors say,
"To talk of many things:
Of liver viruses — and oral bacteria — and slipped —
square knots —
Of hurt knees — and of tumors inside tracheal rings —
Of atopic dermatitis from citric and malic acid intolerance —
Of ureteral achalasia, and testicular surprises, and polysyllabic parlance,
Such as scintiangiographic identification of Foix-Alajouanine syndrome —
And Corynebacterium Parvum,\an anaerobic bacterium little known —
And nonsteroidal anti-inflammatory drugs —
And boat people held together by hugs —
And why figure skaters have hammer toes —
And whether we should pull the plugs."

The Editor Does His Thing

What the authors are trying to say is that this issue is a *parvum opus* – a smorgasbord of short articles about small things. Small things, the purists may say, should not clutter up a quality journal. But small things, humanists and intellectual curiosity seekers among us know, make a difference, especially when the small things are strange diseases, unusual lesions, and rare therapeutic happenings that are doing harm to patients.

Viruses Have Their Day

Consider, if you will, hepatitis viruses.

The hepatitis B virus, or Dane Particle, is 42 nanometers, or one billionth of a meter, in diameter — so small you need an electron microscope to see it. The hepatitis A virus is even smaller — measuring only 27 nanometers.

Yet these tiny viruses, as Osterholm and Andrews discuss in an article in this issue, cause widespread mischief among hospital personnel in Minnesota. Indeed, in a two-year period (1974 and 1975),. 200 cases of viral hepatitis occurred in Minnesota hospital personnel. The ratio of type B hepatitis to non-B hepatitis was five to one. With new hepatitis markers (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis A virus antibody with acute and convalescent phase immunoglobulins), hepatitis A and B should be easier to identify, trace, and treat (when hepatitis B vaccine becomes available).

Skater's Foot Joins the List

Or take "Figure Skater's Foot" — another article in this issue.

I'll wager most of you are on thin ice when it comes to knowing about Figure Skater's Foot. That figures. Well, now you will learn 40 percent of figure skaters have intermittent foot pain, 18 percent have sprained their ankles, and 69 percent suffer from hammertoe deformities.

Why hammertoes? Because young skaters know the tighter the boot, the better control of the blade. But, alas, young feet grow, while boots do not.

Thus, Figure Skater's Foot joins a long list of other recreational and athletic-associated syndromes. If you are prepared for an organ recital, here are some of these syndromes: frisbee finger, tennis elbow, golfer's ear, ski-boot neuropathy, jogger's itch, surfer's knee nodules, sauna pneumonia, surfer's spine; bicyclers' faces injured from shoulder bags; racquet player's retinal detachment; cocktail drinker's lead poisoning from glasses; and, then of course, the palsies: sports-car palsy, bicycler's palsy, skating board palsy, guitar player's palsy, and honeymooner's palsy (or bridegroom's paralysis).

The Spice of Life

From the preceding remarks, you may have gathered I take lightly the articles in this issue. That is not so. This is an excellent issue, full of variegated subject matter. No general purpose medical journal will offer much pleasure or information to its readers unless the journal has variety.

Besides, an occasional issue of this kind offers welcome relief from issues devoted to single subjects, to comprehensive reviews, or to "in-depth" or "integrated,, multidisciplinary studies." I am betting that you, like I, enjoy a return to concrete, specific, and brief articles from varied sources.

Richard L Reece MD

Continuing Medical Education
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Health Care Problems among the Southeast Asian Refugees

"The Boat People"

NEAL R. HOLTAN, M.D., M.P.H.*

ANY CHALLENGING medical problem presents the opportunity for learning. At the present time we are faced with such a challenge and opportunity in meeting the health needs of the Southeast Asian refugees.

A narrative description of those health needs will reflect my own personal experience in St. Paul. Although many of my statements may lack objective proof and others may not be valid for all of the various groups of refugees, a discussion of this experience may be helpful to others. I will delineate the medical needs of one special group of refugees — the Hmong tribe from Laos.

Hmong Tribe

The Hmong migrated from China to the highlands of Laos about 200 years ago. Until recently, their language was an unwritten one. Few members of the nomadic group received Western-style educations. During the War in Southeast Asia, the Hmong supported the United States, serving as ground troops, as rescuers of pilots downed in the mountains, and as an intelligence network. After the war ended, they began to flee to camps in Thailand, where at least 100,000 remain to the present time.

A community of over 1,500 Hmong has congregated in St. Paul, providing the critical mass to attract new refugees and migrants from other parts of the State and from other States. Model Cities Health Clinic at 270 North Kent has provided health care to over 750 Hmong patients. St. Paul-Ramsey Medical Center has registered over 800. Based on this experience, the staffs of both agencies have been able to identify individual health needs among them and to begin understanding some of the broader needs of the entire Hmong community.

Infectious Diseases

Each and every newly-arriving refugee needs to be screened for infectious diseases. Any screening which was done before actual resettlement with American sponsors must be assumed to be invalid. The incidence rate for tuberculosis in St. Paul's refugees, for example, is about 400 per 100,000 per year as compared with nine per 100,000 for the city as a whole. About 25% of the refugees have parasitic infections with *Giardia,* hookworm, *Ascaris, Trichuris,* amoebae, tapeworm, *Strongyloides,* and *Clonorchis* in approximately that order of likelihood. Although the rate of amoebic infection does not appear to be much higher in the refugees than in Americans, two cases of amoebic dysentery have been diagnosed among them. Eosinophilia is often a clue to the presence of helminthic infections.

Information on incidence of gonorrhea is less readily available, but it is the sense of those who have examined many refugees that the rate seems to be about the same as in Americans. No instances of penicillin-resistant Niesseria have been identified in St. Paul. There have been about five cases of syphilis, one case of typhoid carrier-state, and one case of leprosy in the city's refugees.

Other Medical Problems

Besides these more unfamiliar infectious diseases, there are many other medical problems which are easily identified. In children, there seems to be a very high incidence rate of upper respiratory infection, especially otitis media. In adults, one of the major problems is war wounds, mostly shrapnel injuries. There also seems to be a significant amount of gout and hypertension, the latter usually developing after arrival in Minnesota. All ages have nutritional problems due to the many hardships of the past years and the present unavailability of familiar foodstuffs. Cultural attitudes such as eschewing cold foods during the first post-partum month can lead to undernutrition of nursing mothers. Twenty of the first 37 deliveries of Hmong babies in the Maternal and Infant Care Project were deemed high-risk. Hmong women seem to have a fair amount of sophistication about the various methods of birth control and often request alternatives to oral contraceptives.

Community Needs

Arising out of these individual needs, and modified by the cultural systems of the Hmong and the

---

*Model Cities Health Clinic; the Department of Medicine, St. Paul-Ramsey Medical Center, St. Paul, Minnesota; and the Department of Internal Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

Americans, are several community needs. There is a crucial need for interpreters who can translate in the clinic or hospital. It has been observed that the most effective interpreter in the city is a person who had training as a native health aide in Laos. She is functioning as an advocate more than as an interpreter. This advocacy is important, because concepts of health and illness cannot in any instance be assumed consistent between the Hmong patients and the American providers. The differences become critical in emergency or life-threatening situations. On occasion, serious misunderstandings, indeed, the wrath of the entire Hmong community, have resulted from not recognizing these differences or from not being able to communicate with them effectively. The Hmong are wary of becoming labeled as health threats, perceive themselves as being healthier than Americans, and, except for the infectious diseases, are undoubtedly correct.

Organizational Problems

Opposite to the needs of the refugees and the refugee community are organizational problems in the American system of health care which are now being addressed and corrected. Awareness of the health needs of the refugees has taken time to develop. Health screening, up to now rather haphazard and fragmented, is being made more routine and efficient. The crucial need that screening be meshed with a system of primary care is being accomplished either by screening as a first visit to a primary care clinic or by a system of referral from a screening site to a primary care facility. Patient and information flow to the secondary referral system is less well organized at present. The capability of follow-up care and home care is under development. One need that has baffled the usual health care providers in St. Paul is the alleviation of mental health and cultural adjustment problems in the refugees. Obtaining participation and feedback from the Hmong community in general has not been accomplished as yet.

All in all, the Hmong refugees are a healthy group of individuals who pride themselves on their good health and on their willingness to cooperate with the doctor or nurse. Providing medical care to the refugees is remarkably pleasant due to this unique degree of compliance. Once the infectious diseases have been remedied, the ongoing medical problems are very similar to those of other Americans.

In my opinion, coordination of services will require special sources of funds in the next twelve to thirty-six months. Existing service providers simply do not have sufficient time to undertake special programs in addition to their regular duties. But, the two vital elements of good health care for the refugees, coordination of services and health education, will return many long-range benefits to them and to the health care system itself.

My thanks to C. Vang, J. Tolar, R.N., D. Schmidt, R.N., and Drs. D. Thron, P. Garske, C. McKay, and L. Edwards, who must take the credit for any meritorious ideas in this paper.

The Board of Trustees of the Minnesota Medical Association has established an Ad Hoc Committee on the Boat People. This committee is charged with the responsibility of studying all the facts, communicating with the involved government agencies, and initiating a program to assure adequate medical care for the "boat people" who settle in Minnesota.

Many physicians have been rendering free care to the "boat people" and many will continue to do so. If appropriate, we urge physicians to extend this voluntary care. You should be aware, however, that "boat people" are eligible for Medicaid for up to three years upon their application for assistance.

The goal of the Minnesota Medical Association is that "boat people" receive the best possible medical examinations upon arrival and that any necessary treatment be provided. The health of the "boat people" is important not only to the "boat people" themselves, but also to our present population. There is always the risk of exposure to infectious diseases to be considered.

The Minnesota Medical Association will continue to work to improve conditions for the "boat people," to coordinate with government agencies, and to inform you of developments which effect the medical care of these new residents of Minnesota – the "boat people."

Septicemia and Pleural Effusion from Eikenella Corrodens

A Normal Mouth Inhabitant

PAUL STIEGLER, M.D.*

Eikenella Corrodens, normal mouth inhabitant, can cause local and distant infections resulting from dental manipulations. A patient is presented with septicemia and pleural effusions secondary to dental extractions.

LATELY INCREASED interest has been focused on the pathogenicity of a normal oral bacteria — Eikenella Corrodens. Previously known as Bacteroides Corrodens, this organism readily enters the blood stream after dental surgery and has been associated with many local and distant focuses of infection. A case is reported of a patient who developed E. Corrodens septicemia and pleural effusion after dental extractions. This would be one of the rare cases reported to have involved the lungs.

History

A 71-year-old white male presented to his local doctor with malaise, fever, chills, slight non-productive cough three weeks after having all of his upper teeth removed. Physical exam was negative except for mild labored respirations, temperature of 103°, and occasional right lower lobe rales. There was no adenopathy or organomegaly. There was no history of travel, medications, environmental lung exposures, weight loss, TB or allergies. Patient had a 60 pack year history of smoking. Also vocal cord carcinoma was treated with local excision and radiotherapy two years ago. Review of systems was entirely negative.

Chest Xray showed right lower lobe infiltrate, white blood count was 30,100 with left shift, and cultures of blood and sputum were negative. After trial of IV Penicillin the infiltrate resolved but fever and chills continued, despite changing antibiotics to Staphicillin and eventually a combination of Penicillin and Gentamicin. After two weeks in the hospital repeat CXR showed right pleural effusion, and patient was transferred to MMC.

On presentation patient was still spiking temperatures to 103° daily. Right lateral decubitus CXR showed right pleural effusion. Erythrocyte sedimentation rate was 131 and PPD was negative. Pleural fluid showed exudate with 13,000 WBCs (50% PMNs) but cultures were negative.

One week later blood cultures from admission finally grew out Eikenella Corrodens in two separate bottles, one of which also grew a microaerophilic alpha strep non group A, B, or D. Sensitivities of the E. Corrodens showed resistance to both Penicillin and Gentamicin but sensitive to Ampicillin, Carbenicillin, Chloramphenicol and Tetracycline. Ampicillin and Carbenicillin were then started intravenously with rapid defervescence of fever and resolution of chills over the next two days. After two weeks of this therapy, antibiotics were changed to only oral Ampicillin, and patient was discharged. Repeat blood cultures on day of discharge were negative after 10 days.

Discussion

Eikenella Corrodens is a facultative anaerobic gram negative rod that has recently been found to be a primary organism in many different infections. A normal inhabitant of the mouth, E. Corrodens has

Figure

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*Family Practice Hennepin County Medical Center, Minneapolis.

al,[13,14] proposed the organism to be transferred to a new genus Eikenella, in honor of M. Eiken who did the original studies on the organism in 1958.[11] The organism has a different DNA-base composition of bacteroides and hence the genus change. The name "corrodens" refers to the characteristic colonies formed on agar which show a depression or "corroded area" instead of a normal raised colony. The organism grows better in a CO-2 environment and has a smell like laundry bleach (hypochlorite). A fastidious organism — it usually takes at least 48 hrs. to grow, and, as seen in our case, sometimes up to a week.

The organism has now been associated with many different infections, including cellulitis[3] osteomyelitis,[3] brain abscess,[9] endocarditis,[10] abdominal abscesses, and even liver[6] and pancreatic,[7] abscesses. The cultures are usually pure but it has also been grown occasionally with non A B or D streptococcus. Interestingly in our patient one of the blood cultures of E. Corrodens was accompanied with this streptococcus. The significance of the strep was shown by Brooks et al.[2] when evaluating abscesses of E. Corrodens in drug addict patients using Methyl phenidate. They injected rabbits subcutaneously with Methyl phenidate and E. Corrodens, but no abscesses formed. However, when adding streptococcus to the above mixture significant abscess formation occurred.

Antibiotic sensitivity to E. Corrodens is usual to Penicillin, Ampicillin, Carbenicillin, Tetracycline, and chloramphenicol. High doses of Aminoglycosides are needed and therefore should not be used. Resistance to Cephalothin is variable and marked to Methacillin. Of clinical importance is the marked resistance of Eikenella to Clindamycin which is usually very affective against anaerobic infections. Interestingly, our organism was resistant to both Penicillin and Gentamicin.

Therefore, as we have seen, Eikenella corrodens, known habitant of the mouth and upper respiratory tract has been implicated in many varying infections. This case was presented to show a new variant of the clinical picture so far seen with Eikenella. Although the culture from the pleural fluid never grew out Eikenella, the positive blood cultures and the clinical picture in this patient with the timing of the oral surgery seem to fit for a resultant pneumonia from septicemia by the Eikenella. The history, pathogenesis, clinical picture and treatment have been discussed and now it remains for us to think of this organism in infections which may be associated with previous oral manipulation.

Summary

A 71-year-old smoker presented with malaise, fever, chills, and productive cough three weeks after multiple dental extractions. Chest Xray showed a right lower lobe infiltrate, a blood culture grew out Eikenella Corrodens — a facultative anaerobic organism normally residing in the mouth.

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Atopic Dermatitis

Associated with Citric and Malic Acid Intolerance

WILLIAM E. WALSH, M.D.*

The relationship of atopic dermatitis and intolerance to citric and malic acids was studied in 34 patients. All patients had positive 48-hour patch tests to citric acid or malic acid [or both]. Eliminating foods with high concentrations of citric and malic acids improved the dermatitis. Challenge with these foods caused it to worsen.

A PREVIOUS REPORT described the use of food patch tests in patients with dermatitis.[1] Two patients reacted positively to citric acid and responded to a diet low in citric acid. Since that time a total of 34 patients with positive reactions to citric acid or malic acid [or both] have been investigated and they are the subject of this report.

Material and Methods

Patients

Patients were referred by their primary physicians for evaluation of significant allergic diseases. All had atopic dermatitis, with a dry, excoriated, and pruritic rash.[2,3] There was erythema in association with acute disease and lichenification with skin thickening in chronic cases. Patch testing was employed if the history revealed no obvious cause of the dermatitis. Four patients were excluded who did not return for follow-up.

Diet

The test diet avoids processed foods and beverages in which citric and malic acids are used in significant quantities to enhance flavor. All vegetables are allowed except potatoes, tomatoes, cauliflower, and lima beans. All fruits are excluded except fall and winter apples, pears, bananas, and melons.

Patients were instructed to follow this diet carefully for two weeks to observe the effect of avoidance. During the third week they challenged themselves with a diet high in citric and malic acid until their dermatitis flared.

Patch Tests

Citric and malic acids are applied as a 10% solution in water with the use of Al-Test† occlusive patches.[4] The test patches are removed at 48 hours and the results are read as follow: erythema 1+, erythema and papules 2+, erythema, papules, and edema 3+, and erythema, exudation, and crusting 4+.

Results

The dermatitis was similar in all age groups, the youngest patient was 5 months old, the oldest 46 years old (Table). It could begin at birth or years later. The rash was persistent, many patients were affected for years.

Two patterns of involvement were present. In one pattern the dermatitis was limited to the extremities sparing the trunk, the other was distributed over the body surface. Neither age nor the degree of reactivity to patch testing appeared to influence the distribution.

Associated allergic conditions are common in atopic dermatitis. They are common in this group of patients as expected. Both immediate reactions [seasonal allergic rhinitis and urticaria] and delayed reactions [contact dermatitis] were present. Contact dermatitis involved such familiar antigens as mercury, wool, neomycin, parabens, balsum of Peru, and nickel.

Patch tests proved to be reliable. When they were positive, avoidance of foods high in citric and malic acid improved the dermatitis; with challenge the rash flared. When the test was negative, no response to diet was noted.

The size of the reaction on patch testing was useful in predicting the sensitivity of patients to citric and malic acids in their diets. When patients challenged themselves, patients with 1+ reactions found they could tolerate larger quantities of citric and malic acids than patients with 4+ reactions. Many patients have been followed for several years and their level of sensitivity remains unchanged.

Use of both citric and malic acid for testing allowed the identification of more patients than was achieved by the use of either alone. Although 18 patients reacted to both, 10 patients reacted only to citric acid and six only to malic acid.

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†Hollister-Stier Laboratories, Division of Cutter Laboratories, Inc.

Discussion

This report was delayed by the hesitation to report without additional investigation what may be a new disease. I am not aware of previous reports indicating that citric or malic acid can produce skin disease. Since citric and malic acids are intermediates in the Kreb's citric acid cycle, a defect in this cycle may be at fault. This also has not been reported. However, when so many patients responded well to testing and diet, it became necessary to report this experience as soon as possible. Other physicians may find it valuable in the management of patients with atopic dermatitis.

Citric and malic acids should be harmless chemicals. Not only are they widely distributed in the foods we eat, but as part of the Kreb's cycle they are normal constituents of the body and essential for survival. It is remarkable that they can cause such a persistent and uncomfortable dermatitis.

We have noted the frequency of allergic disease in atopic dermatitis that implies that citric and malic acid intolerances are also allergies. However, these substances do not appear to act as classic allergens, for the following reasons:

1. Allergens should be foreign to the body. These chemicals are not foreign and should not provide an immunologic reaction. For similar reasons, they probably do not form good haptens.
2. Patch tests are used in the diagnosis of delayed hypersensitivity.[4] Their use in this study seemed to indicate that intolerance to citric and malic acids is a delayed hypersensitivity reaction; however, the absence of vesiculation in both the patch tests

TABLE

Characteristics of Patients and Response to Patch Tests

Patients	Age	Duration of Dermatitis	Coexisting Allergic Conditions*	Location of Rash	Reactions to Patch Tests (1-4+) Citric Acid	Malic Acid	Succinic and Fumaric Acids
1	5 months	1month		Generalized	1+	0	S4+
2	10 months	9 months		Generalized	1+	0	
3	2 years	18 months	CD	Extremities	0	4+	
4	2 years	1 year	U A	Generalized	3+	0	
5	2 years	1 year	PR CD A	Generalized	2+	0	
6	2 years	2 years	PR U	Generalized	4+	4+	
7	2 years	2 years		Extremities-Face	2+	2+	
8	3 years	1 year		Extremities	3+	3+	
9	4 years	4 years	PR CD SR	Generalized	3+	0	S3+
10	5 years	2 years	SR A	Generalized	3+	3+	
11	5 years	3 years		Generalized	4+	3+	
12	9 years	9 years	CD U	Extremities	2+	2+	
13	10 years	10 years	PR U A	Generalized	4+	3+	
14	10 years	10 years	U	Generalized	2+	2+	
15	14 years	12 years	PR	Generalized	2+	2+	
16	15 years	15 years	SR A	Extremities	2+	2+	
17	20 years	1 month	PR A	Generalized	2+	2+	
18	20 years	20 years	CD U SR A	Generalized	0	4+	
19	20 years	5 years	PR SR	Extremities	1+	1+	
20	20 years	20 years	CD U SR A	Generalized	0	4+	
21	21 years	19 years	U SR A	Generalized	3+	2+	
22	22 years	10 years		Generalized	4+	0	
23	22 years	20 years	U SR A	Generalized	2+	2+	
24	24 years	10 years	CD	Extremities	3+	2+	
25	25 years	1 year	CD U A	Generalized	3+	3+	
26	27 years	27 years	CD SR	Extremities	4+	0	
27	28 years	15 years	CD SR	Extremities	2+	2+	
28	29 years	5 years	CD	Extremities	2+	2+	
29	34 years	1 year	CD	Extremities	0	3+	
30	35 years	30 years	PR U SR A	Generalized	3+	0	
31	37 years	37 years	PR U A	Extremities	1+	0	S1+
32	37 years	3 months	PR	Extremities	0	1+	
33	38 years	15 years	PR U SR	Extremities	4+	0	F1+
34	46 years	10 years	A	Generalized	0	3+	

*CD — Contact Dermatitis

U — Urticaria
*PR — Perennial Rhinitis
SR — Seasonal Rhinitis
*A — Asthma

and the dermatitis appears to separate this reaction from that of delayed hypersensitivity, in which vesiculation is prominent.

3. Allergic reactions can be provoked by minute quantities of antigen. In this group of patients, only the most sensitive experienced dermatitis from small quantities of citric or malic acid. In others, dermatitis developed only after ingestion of large quantities.

These factors suggest that this intolerance does not represent classic allergy. If there is a relationship between allergy and citric and malic acid intolerance, its basis is unknown.

As mentioned above, citric and malic acid intolerance may be due to a defect in regulation of the Kreb's cycle. Malic acid, an intermediate in the cycle, was added to the test because of this possibility and proved very valuable. Fumaric and succinic acids, other intermediates, were also used. Their poor solubility in water made their value questionable, although one patient reacted to fumaric acid and three responded to succinic acid. In contrast, citric and malic acids dissolve readily, and this may be the reason they perform well in patch tests.

The use of acidic patch-test material on atopic skin raises the question whether these reactions are false positive and are due to irritation. However, the test was negative in nonatopic controls. Ascorbic acid, used as a control, did not cause a reaction. Multiple patients with atopic dermatitis indistinguishable from this group were tested; they had negative reactions to the patch test and the diet. These factors indicated that the acidity of the test materials does not explain the results.

Positive patch tests were often obtained from skin areas not involved with dermatitis. They were negative in many patients whose whole body dermatitis forced the application of the tests to affected areas. Therefore, positive tests could not be explained by the condition of the skin site used for testing.

This report describes an approach to diagnosis and treatment of some patients with atopic dermatitis. It does not adequately emphasize the difficulty of working with this group of patients. The diagnosis of atopic dermatitis is difficult, particularly in the presence of infection, urticaria, or contact dermatitis. Often, testing must be delayed until the skin problems are brought under control. In some cases, the test appears to aggravate the dermatitis. Repeated testing is often needed before a clear result is obtained.

These patch tests should be used by physicians skilled in the investigation of eczema. Without adequate experience, the diagnosis, testing, and therapy may be inadequate. Then the proper approach becomes confused, the rash worsens, and the patient becomes resistant to appropriate diagnostic tests and therapy.

If properly applied, patch tests with citric and malic acids can identify intolerance to these chemicals among patients with atopic dermatitis. This reduces reliance on the cumbersome and error-prone elimination diets that must be used when diagnostic tests are not available.

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The "Square Knot" That Slips.

JOHN STRICKLER* and PAUL G. GANNON, M.D.†

Dr. Paul Gannon, my clinical tutor during my phase B (sophomore) surgery rotation, pointed out that some of my "square knots" were improperly thrown. Despite tying knots as I thought "the book" indicated, the resulting knots sometimes looked like, and acted as, slip knots. Other medical students and physicians who infrequently tie sutures might be interested in the potentially dangerous possibility of unwittingly transforming a "classic" square knot into a slip-type knot.

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*Phase D-4 Medical Student, University of Minnesota, Minneapolis.

† Minneapolis cardiovascular surgeon and Clinical Professor, University of Minnesota, Minneapolis.

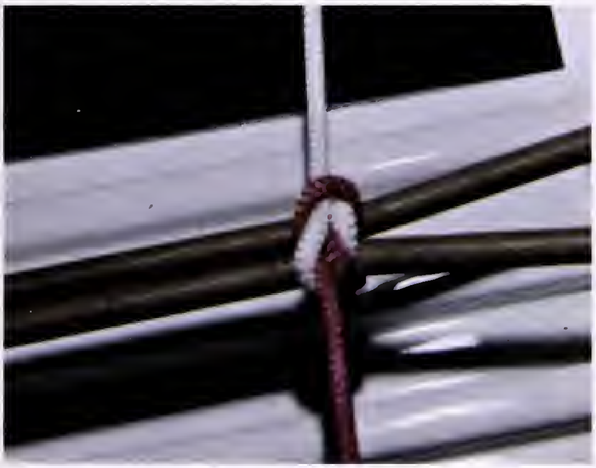

Fig. 1 — The square knot, when tied properly, provides good friction for reliably holding under tension.

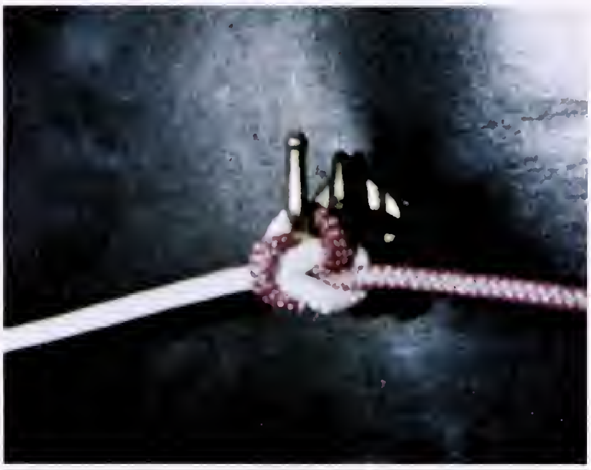

Fig. 2 — It is also reliable for tying off vessels.

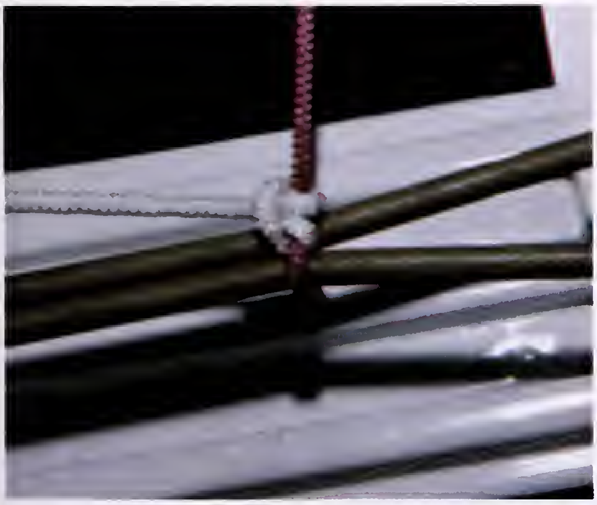

Fig. 3 — However, with fine suture material, we don't see how the knot lies. It is remarkably easy for a beginner to throw the knot shown in this Figure. This is not a *granny* knot. It *is a square knot* in all ways except the way tension was applied. In fact, the "classic" square knots in frames one and two can be *transformed* to this knot by merely pulling one line while the other line is relatively slack.

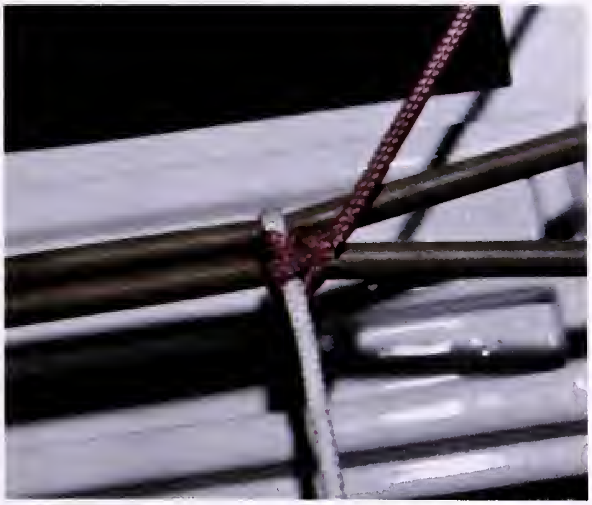

Fig. 4 — *Either* line can easily become straight if:

a. the alternate throws are not tightened in opposite directions
b. the knot is not tightened with equal tension on both lines
c. a single handed knot is thrown (in times when safety is important) by any but the most experienced person.

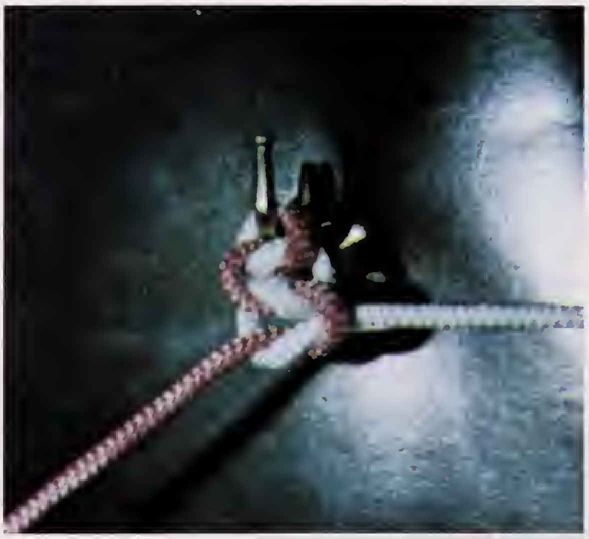

Fig. 5 — This problem also exists for multiple thrown knots.

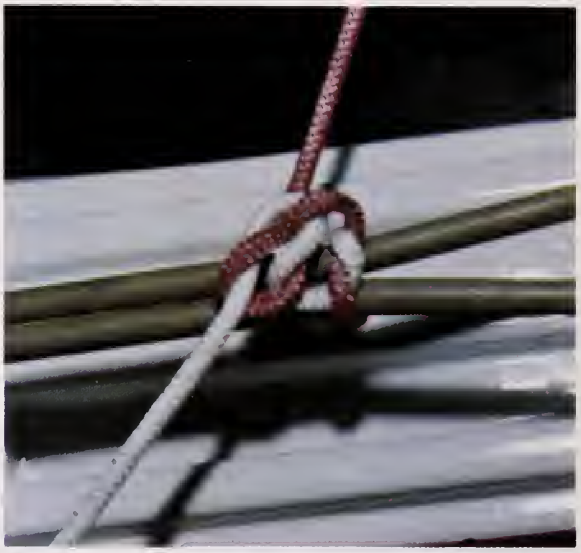

Fig. 6 — Even if each throw is done with tension in the correct direction, a relatively loose knot can be easily . . . . (Figure 7)

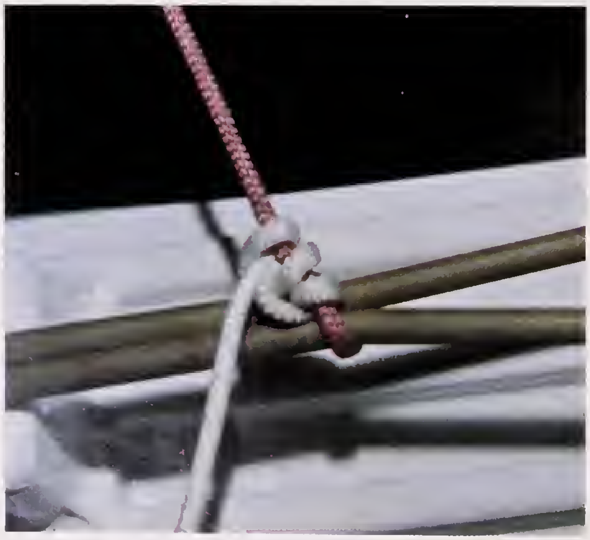

Fig. 7 . . . transformed into a "dangerous" knot by pulling either line harder than the other line.

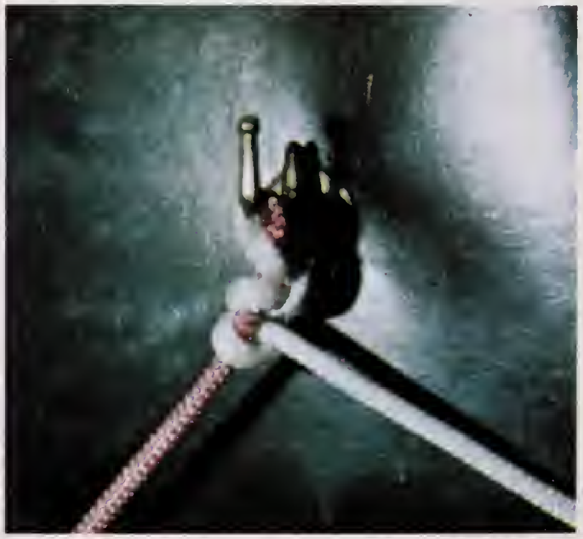

Fig. 8 — This danger is particularly serious when tying off vessels.

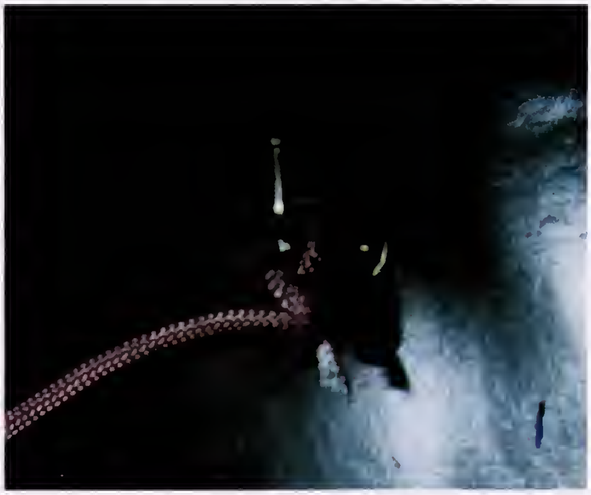

Fig. 10 — Even multiple throws "around" a straight line are unsafe.

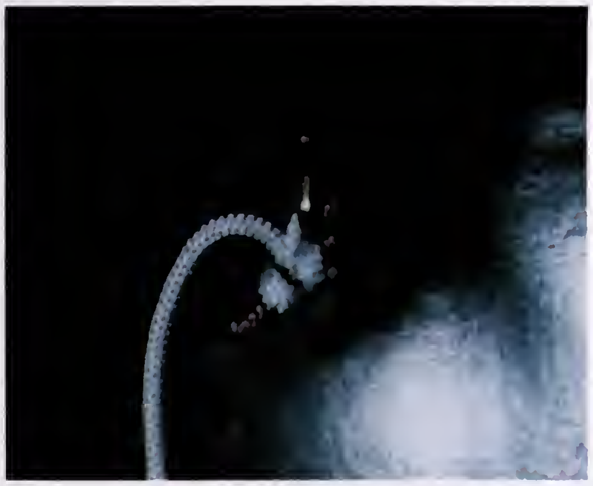

Fig. 9 — The friction on the "straight line" of the knot is insufficient. When the long ends are cut, the "straight line" could slip out of the knot.

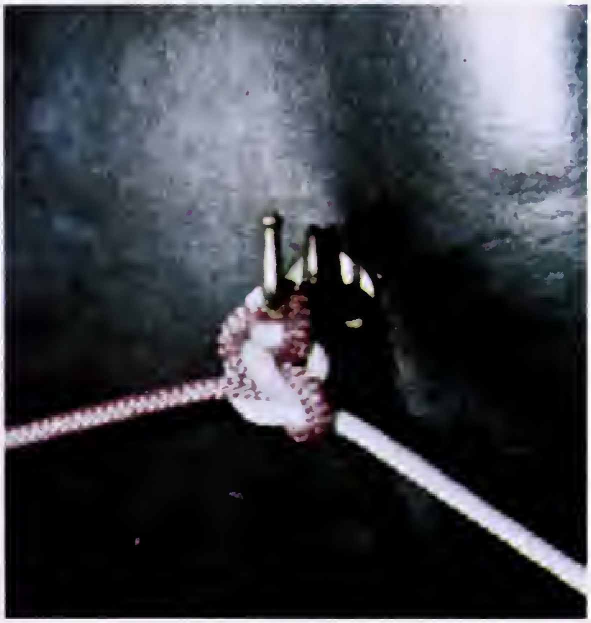

Fig. 11 — It is a good idea to learn knot tying with a line which is large enough for you to easily see the results of your technique. This is particularly true when learning one handed knots.

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Figure Skater's Foot

MICHAEL W. DAVIS, M.D.* and THOMAS LITMAN, M.D.*

Forty-five competitive figure skaters were studied. 40% had intermittent foot pain severe enough to interfere with skating. 18% had sustained ankle sprains. 69% had hammertoe deformities. It was felt that these problems were associated to some degree with the choice and fit of the skating boot.

SEVERAL FIGURE SKATERS have been recently seen in our office with lower extremity problems. A search of the literature failed to reveal any information regarding this association.

Competitive figure skating in the United States is governed by the United States Figure Skating Association. There are 400 member clubs and approximately 38,000 skaters registered by the USFSA. While there are some men involved, active competitors at all levels are for the most part women ranging in age from seven to nineteen. Depending on their talent, motivation and financial reserve these individuals spend up to six hours a day, six or seven days a week on the ice. Some forego public school for private tutors. Devotion to the sport may go to great lengths, affecting both the skater and her family.

The successful completion of USFSA tests marks the progress of the skaters and provides eligibility for competitive events. There are annual Regional, Sectional and National Championships of the United States. These are steps leading to qualification for international competition including the Olympic Winter Games and World Championships.

The Figure Skating Boot

The modern figure skating boot may be obtained in both stock and custom made models. Stock boots which are purchased off the shelf vary in quality and price. Custom boots are available for the skater who requires or demands a closer fit. Measurements of the individual's feet are obtained and the boots are handcrafted to these measurements, a process which may take from two to eight weeks. The customer may request a soft, firm, or extra-firm upper reinforcing. The blade is purchased separately and selected according to intended use (i.e. free skating and compulsory figure blades are designed somewhat differently).

Material

We interviewed and examined forty-five female figure skaters from the Minneapolis area. All were registered with the USFSA and all were actively engaged in preparation for both testing and competitive events. Their age range was from nine to eighteen with a mean age of 13.5.

History

The skaters and often their mothers were questioned regarding foot or lower extremity problems prior to beginning the sport. None had a significant prior history. We then asked if there had been lower extremity difficulties associated with skating. Eighteen(40%) complained of intermittent foot pain severe enough to require medical consultation or periods off the ice. Six of this group were wearing orthotics prescribed by a podiatrist. Eight (18%) had sustained ankle sprains. Nine girls (20%) had a history of Osgood-Schlatter's disease treated by rest only. One girl had suffered a stress fracture of the great toe.

Examination: Leg

Lower extremity examinations were conducted on each skater. The entire leg was evaluated for range of motion, ligamentous stability, presence of varus, valgus or torsional deformities, and muscular strength and development. Generally the examination from hip to lower tibia was normal. A minimal tendency toward lateral collateral ligamentous laxity in several knees was noted. Gluteus and quadriceps musculature was extremely well developed, both in strength, mass and definition. Hamstring and calf musculature while excellent, was less striking.

Examination: Ankle

Most of these girls (91%) had a palpable hypertrophy of the anterior tibial tendon in front of the ankle. An overlying callus was usually present but this did not seem to be tender, nor was it a source of discomfort for the skater. The posterior tibial tendon was also hypertrophic and quite prominent behind the medial malleolus (84%). Some skating mothers characterized this medial ankle area as "the double ankle bone that skaters get." This was occasionally associated with a callosity but seemed to cause no discomfort.

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*Minneapolis, Minnesota.

Examination: Foot

The greatest problem area was the skater's foot. Hammertoe was the most common deformity and one or more were present in 69% of the skaters. When present, hammertoes were usually multiple and bilateral. There was a tendency for the right foot to be somewhat more involved than the left, both in frequency and severity. (This may be a reflection of a minor foot asymmetry. The average right foot length was 22.9 centimeters and the average left foot length was 22.7 centimeters. The widths of right and left foot did not vary statistically.) Hammertoes could be straightened passively but upon release would immediately return to their deformed position. Hard corns were commonly present over the dorsum of the proximal interphalangeal joints of the affected toes, especially on the dorsolateral aspect of the fifth toe. These deformities were only mildly symptomatic and did not interfere appreciably with the skaters' practice schedule or their enthusiasm for the sport.

Less frequent abnormalities noted were mild bilateral hallux valgus in three girls, a dorsal bunion deformity in one, and a wart on the medial great toe in one. No skaters were found to have abnormal or painful plantar callosities. Occasionally we saw a "beat-up" right great toenail (this is the foot generally used for the more vigorous toe jumps) but no permanent toenail abnormalities were evident.

Analysis

These girls began skating at an average age of 6.7 while even the youngest girls had hammertoe deformities, their number and severity did tend to increase as the skating years went by. A similar relationship existed between hammertoe deformities and the hours per week spent on the ice. This varied from seven to forty-eight (the latter in a U.S. National Competitor) and averaged nineteen.

Twenty-seven (60%) of the skaters used stock boots and eighteen (40%) used custom boots. This choice did not seem to effect the presence or absence of foot problems. Half of the skaters selected boots with soft uppers, and the other half chose firm reinforced uppers. No correlation was evident between firmness of the boot and foot deformity, but there was a strong tendency for the skaters using the heavier boot to suffer from intermittent foot and ankle discomfort and to have more frequent ankle sprains.

Discussion

Competitive figure skaters are generally a devoted and enthusiastic group of elite athletes. Involvement begins at a young age and can become a total commitment. Long hours are spent on the ice perfecting both free skating and compulsory figures.

The skating boot is chosen and fitted with care. It is widely felt (and perhaps with validity) that the tighter the boot, the better the control over the blade. Therefore, both stock and custom boots are selected to fit snugly with only a nylon stocking or skating tight over the foot. This fit may not be detrimental initially but the skater's foot grows and the boot remains the same size. Time between measurement for custom boots and their fabrication aggravates the situation. As the months progress the foot becomes increasingly cramped, and since the average skater changes boots only about once a year, hammertoes and corns are the result. The deformities are slightly more common and pronounced on the right foot, since the right foot is usually a bit longer than the left. While the contracted toes correct passively and cause little discomfort in youth, it is anticipated that with the passage of time the deformities will become more fixed and symptomatic. The answer to this problem would seem to be fitting the boot less snugly to begin with, at least in the toe box area, and changing to a larger boot as the foot grows.

The extra-firm reinforced boots are associated with an increased incidence of foot strain and ankle sprains. They are too heavy and unyielding for these young feet. The softer boot is less traumatic and more readily tolerated for long hours of skating.

Achalasia of the Ureter

MICHAEL BJORK, M.D.*

The term achalasia ("failure to relax") of the ureter is of historical interest only. A myriad of terms have been used to describe the relatively uncommon entity characterized by functional ureteral obstruction (usually distal) caused by an adynamic segment of ureter of varying length. The ureteropyelocalyceal system proximal to this area of obstruction shows different degrees of ectasia. By definition, there is no vesicoureteral reflux, no extrinsic or intrinsic obstruction to the ureteral lumen, no bladder outlet obstruction, no neurogenic bladder dysfunction, and no abnormalities of the bladder wall, trigone, or orifices. This discussion will summarize the clinical, radiological, anatomical, and histological features of this entity. An attempt will also be made to clarify the various theories regarding the basic underlying pathophysiology and finally, current concepts on therapy, both surgical and conservative, will be reviewed.

THIS PROCESS IS usually a progressive disease of early life, probably of congenital origin.[10] However, the age of diagnosis varies and it can be an incidental finding in the elderly. The disease tends to be more stable in adults, but it can be deceivingly unimpressive and warrants close follow-up. There is a unilateral, left-sided preponderance with males being involved more commonly than females. Associated congenital anomalies outside of the genitourinary tract can be present.[13,16] The presenting renal function studies are usually within normal limits but can deteriorate if the disease is rapidly progressive. Common associated findings include urinary tract infection (usually recurrent), gross or microhematuria, and recurrent flank pain with or without calculi.[3,7,12] Non-specific complaints can predominate. Flank or abdominal masses are uncommon.

Anatomical and Radiological Features

The adynamic segment is usually juxtavesical in position but can be more proximal.[14] The segment can be from a few millimeters to several centimeters in length, the average being 1.5 — 2.0 cm. The ureter above the affected segment is usually dilated in a fusiform fashion with a sharp or tapered cut-off. The proximal ectasia is of varying degree, from minimal dilatation of 2-3 cm. in length to gross ureteropyelocalyceal dilatation (although the latter is uncommon) (Figures 1A and 1B). The lumen though the adynamic segment is of normal caliber, allowing easy passage of a 5-6 Fr. ureteral catheter. Retrograde

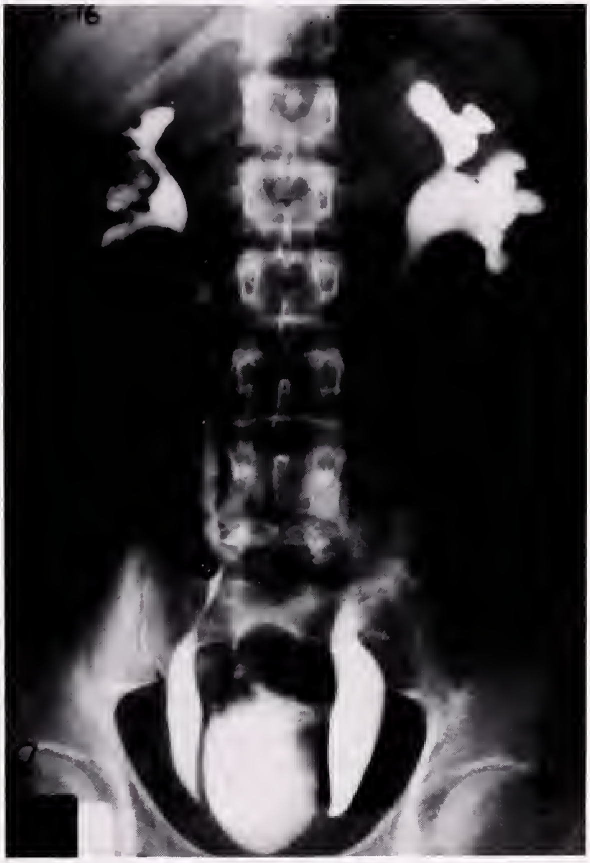
Fig. 1(A) — This film demonstrates a bilateral case of adynamic distal ureteral segments with minimal proximal ectasia on the right and a moderate degree on the left.

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*Resident in Urology, Hennepin County Medical Center, Minneapolis, Minnesota. Presently practicing in Colorado Springs, Colorado.

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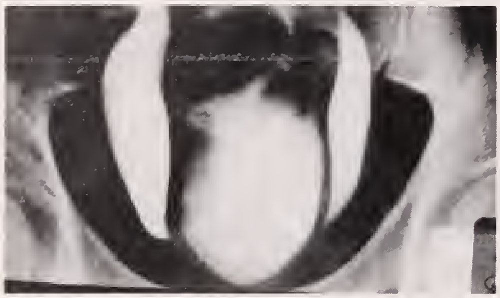

Fig. 1(B) — A closer view of Figure 1(A). Note the tapered cut-off of the dilated proximal ureter above the adynamic segment. Also note the narrow stream of dye being forced through the adynamic segment.

pyelography can be used to fully delineate the adynamic segment and the proximal ureter (Figure 2). There is no reflux on voiding cystography and the endoscopic findings are normal. Cinefluorography can be used to demonstrate normal ureteral peristalsis down to the level of the adynamic segment. At this point, peristalsis markedly decreases but does not completely cease (small amounts of urine are forced through this area). No physiologically active reverse peristaltic waves have been identified.[12]

Pathophysiological Theories

Prior to 1967, theories hypothesized a lack of neuronal elements in the adynamic segment. Reports since then have discounted this concept.[1,9,10,14] The current debate concerns the amount and configuration of the smooth muscle present in the adynamic segment.

Creevy[1] (1967) stated that there was an abnormality of the musculature (usually hypertrophy) in the functionally obstructive segment, but did not further elaborate.

MacKinnon, et. al.[9] (1970) studied this area in detail. Pathological specimens included the ureteral orifice, intravesical ureter, adynamic segment, and a portion of the dilated ureter proximal to the obstructive segment. Their conclusion was that there was an absence or marked decrease of musculature in the adynamic segment.

Tanagho, et. al.[14] (1970) performed a similar study but with more detailed cross and longitudinal sections. Their conclusion implicated an abnormal configuration of smooth muscle fibres in the adynamic segment, with circular fibres predominating. The normal ureter has a syncytial investment of circular, oblique and longitudinal fibres down to the intravesical ureter which is exclusively made up of longitudinal fibres to facilitate shortening during opening of the ureteral orifice. This study found a preponderance of circular fibres in the adynamic segment thus causing a functional obstruction of the peristaltic wave with the degree of obstruction being directly proportional to the percentage of circular fibres.

McLaughlin, et. al.[11] (1973) expanded on Tanagho's theory by discussing other possible disorders of the smooth muscle investment of the adynamic segment. These include mural fibrosis and muscular hypoplasia. They also presented a few cases in which the histological cross sections were apparently normal. These authors stress that the adynamic segment is not aperistaltic but exhibits a limited emptying capacity.

In all of the above extensive studies, the proximal dilated ureter was noted to have hyperplastic circular and oblique muscular elements presumably as a compensatory reaction to the obstructive segment.

Treatment

Conservative treatment can be considered if the degree of proximal ectasia is low-grade, if there is no evidence of renal decompensation, if the presenting

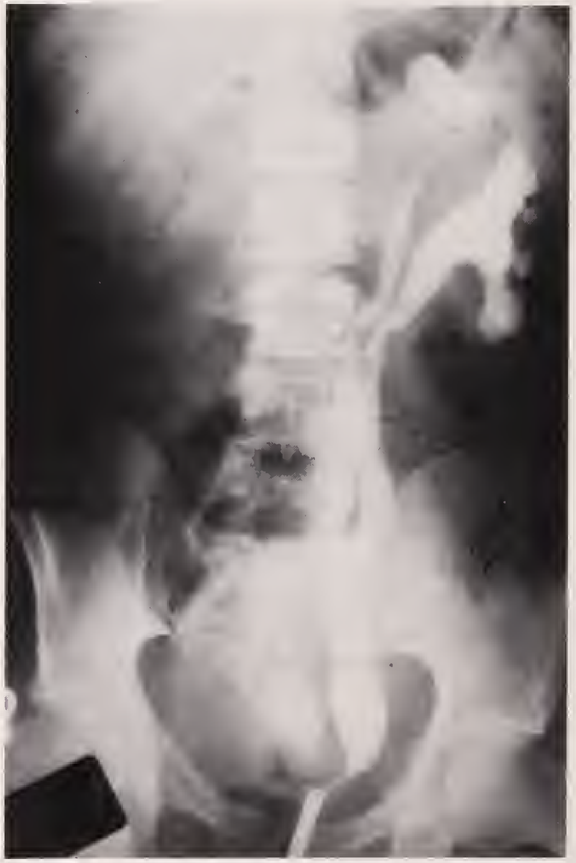

Fig. 2 — This film demonstrates relatively severe proximal ectasia in a partially duplicated collecting system.

symptoms are minimal or not present, if urinary calculi are not present, and if urinary tract infection can be easily controlled with antimicrobial agents. Conservative treatment must be abandoned if the upper urinary tract deteriorates, if infection is recurrent, or if symptoms increase. Urine cultures every three months and IVPs every six to twelve months are suggested due to the high incidence of rapid renal decompensation following initially undetected superimposed infections.[1,3,7,13,16]

Surgical treatment must be immediately considered in patients who do not meet the conservative criteria. Since the Mid-1960s the surgical treatment of choice has been excision of the adynamic segment, with or without tailoring of the dilated proximal ureter followed by re-implantation using an anti-reflux technique (usually the Leadbetter-Palitano technique). Most authors advocate tailoring of the ureter if the ureteral diameter following excision of the adynamic segment is greater than 1 cm. (Hanna and Jeffs[2] use 6 mm. as their criterion). To prevent over-aggressive trimming, this procedure can be done over a 10 Fr. catheter. A ureteral stent is normally left in place 10-14 days postoperatively.[11] Only rarely is a second procedure necessary on the upper tract.[4] Surgical results were considered successful if the ureteral dilatation on IVP improved or at least remained stable and if the patient remained infection free without symptoms. With these criteria in mind, success rates of 60% to 90% have been reported[11,15,16] (Figure 3).

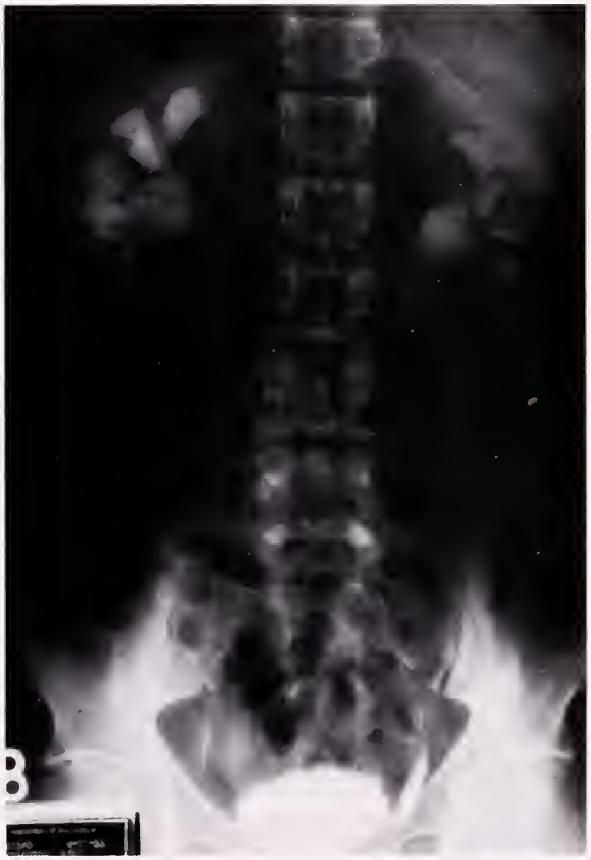

Fig. 3 — Postoperative IVP from Case demonstrated in Figure 1(A). The surgical procedure consisted of excision of both adynamic ureteral segments followed by ureteral reimplantation using the Leadbetter-Palitano technique. Tailoring of the left side was done.

Summary

Functional ureteral obstruction is a relatively uncommon, well-recognized disorder with standardized radiological and gross anatomical features. The disease is generally diagnosed in children who present with gross hematuria or urinary tract infection and exhibits variable degrees of progression, from stable cases to cases of rapid deterioration. The precise etiology remains controversial. The most promising theory implicates an abnormal syncytium of smooth muscle in the adynamic segment (mainly circular fibres with few, if any, longitudinal and oblique fibres). Conservative treatment is advocated in less severe, non-progressive cases. Surgical intervention has been associated with increasingly gratifying results. The treatment of choice being resection of the adynamic segment with or without tailoring of the dilated proximal ureter followed by anti-reflux re-implantation.

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Scintiangiographic Identification of Lesion Producing Foix-Alajouanine Syndrome

CLARENCE E. HENKE, M.D.,* JOHN M. WOLFF, M.D.* and REX B. SHAFER, M.D.*

A patient with progressive central nervous system symptoms was studied by radionuclide scintiangiography when contrast myelography failed to determine the nature of an expanded spinal cord lesion. The scintiangiogram showed localized increased activity in a spinal cord site, suggesting a vascular tumor or malformation At surgery, a large unresectable capillary hemangiomatous tumor was found. Vascular abnormalities of the cervical spinal cord producing the Foix-Alajouanine syndrome are discussed. The need for prompt diagnosis before clinical signs and symptoms become established is emphasized.

A 51-YEAR-OLD CAUCASIAN male with progressive central nervous system symptoms, characteristic of the Foix-Alajouanine syndrome (1926) was referred for a "spinal cord scan." Twenty years earlier he had undergone an extensive laminectomy to correct a "blockage" at the mid-cervical cord level. No specific etiology of this "blockage" was identified. Four months following surgery, the patient began experiencing right leg weakness and associated pain. Soon thereafter he became paraplegic and later developed a neurogenic bladder.

In 1977, the patient was hospitalized with weakness and decreased coordination in his upper extremities. Neurological findings included decreased sensory perception from C-4 through C-7 and absent perception below T-3, right hand grip less than left, flaccid anal sphincter and marked spastic paraparesis. Cervical spine radiographs revealed a laminectomy from C-3, to T-2 with incomplete fusion of the T-1 transverse process. A contrast myelogram showed widening of the upper and mid-cervical spinal cord with overlying, dilated, tortuous surface vessels (Figure 1). A "spinal cord scan" was requested and a scintiangiogram was performed by injecting 20 mCi ^{99m}Tc-DTPA intravenously in the right arm. By eight seconds post-injection, localized activity appeared in the posterior mid-cervical area and persisted for at least six seconds (Figure 2). A highly vascular tumor or A-V malformation was considered as most likely cause for this finding. A spinal cord contrast angiogram showed

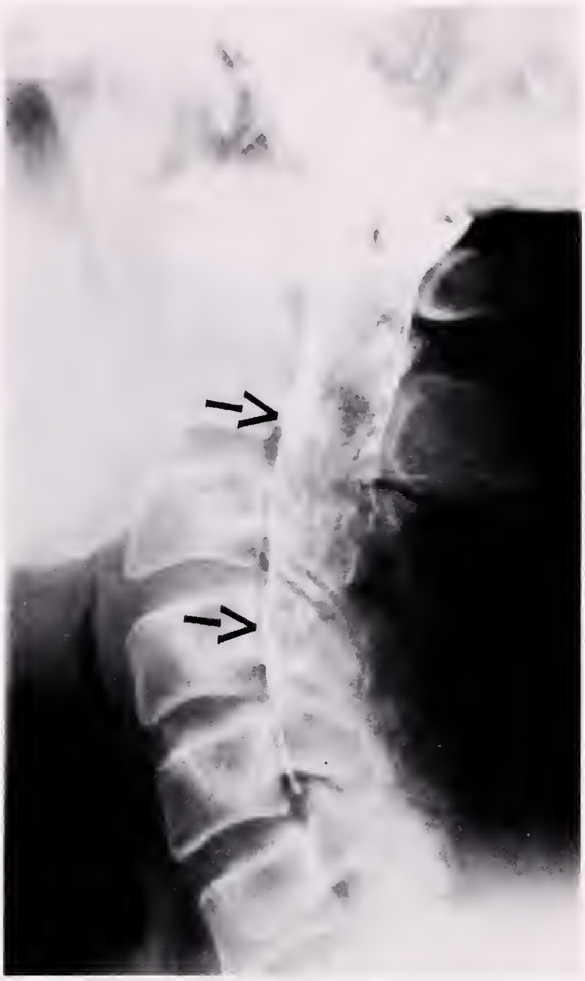

Fig. 1 — Left lateral view of neck. Contrast myelogram shows expanded upper and middle cervical spinal cord with overlying dilated, tortuous vessels (arrows). Some residual Pantopaque™ remains in the upper cervical cord region.

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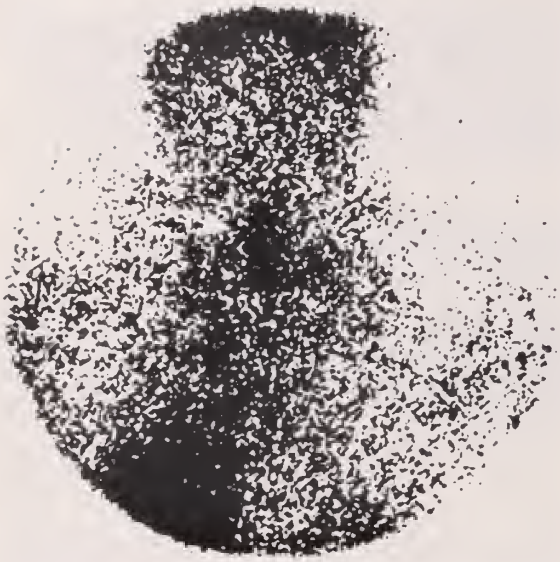

Fig. 2 — Posterior view of head and neck. Scintiangiogram shows increased activity in mid-cervical spinal cord area eight seconds after intravenous injection of 20 mCi ^{99m}Tc-DTPA in right arm (arrow).

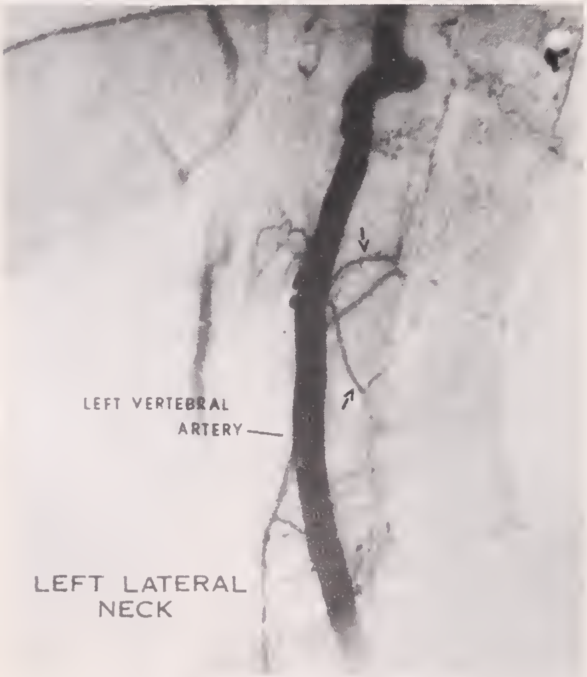

Fig. 3 — Left lateral view of neck. Spinal cord contrast angiogram (subtraction technique) shows several vessels (arrows) from left vertebral artery towards spinal cord. Pantopaque(TM) residual image in subarachnoid space has been subtracted.

several small vessels extending from both vertebral arteries and thyrocervical trunks toward the widened cord area, but no convincing evidence for either a vascular tumor or A-V malformation (Figure 3). These findings were suggestive of an intramedullary glioma with large veins. Thus, the apparent vascular abnormality indicated by the scintiangiogram was not explained and exploratory neurosurgery of the lower cervical cord level was performed. Residual defects from the previous laminectomy limited the operative field, but a large vascular mass in and around the mid-cervical cord level was found. The lesion was considered unresectable and only multiple biopsies were obtained. The biopsies demonstrated a capillary hemangioma grossly; and a mixed-connective tissue vascular lesion by light and electron microscopy. No malignant cells were identified. Radiation therapy of 5,000 rads directed to posterior mid-cervical area was given in an attempt to decrease the lesion size and the patient was discharged to continue with supportive nursing home care.

Discussion

Vascular abnormalities of the cervical spinal cord producing central nervous system clinical signs and symptoms are not common. Hebold (1885) reported the first spinal cord vascular malformation with isolated cases of spinal cord vascular lesions reported thereafter. Guillain and Alajouanine (1925) correlated cord vascular malformations with specific or suggestive contrast myelography findings. The following year, Foix and Alajouanine reported on proliferative, noninflammatory vasculitis and venous dilatation with associated subacute myelitis signs and symptoms, including gradual and progressive spinal sensory loss, abnormal upper and lower motor neuron signs, lower extremity weakness progressing eventually to a flaccid, areflexic paraplegia and increased spinal fluid protein. These findings, identified as a syndrome for a cervical cord vascular malformation producing myelomalacia and myelitis, were confirmed later by Greenfield (1939), Wyburn-Mason (1943), and Antoni (1962).

The clinical signs and symptoms in this syndrome are variable and depend on the degree of compression, ischemia or infarction of the spinal cord. Clinical signs and symptoms are not reliable enough to accurately localize the lesion at a specific cord level according to Antoni (1962). For localization, contrast myelography is the initial study of choice with attention to both ventral and dorsal surfaces of the cord. In about 75% of cases with "characteristic findings" described by

Guillain and Alajouanine, contrast myelography suggests a vascular cord lesion as noted by Aminoff and Logue (1974). Lesion vessel size, number and location determine the diagnostic accuracy of this method as discussed by Gross and Ralston (1959). In the patient reported here, myelography suggested either a vascular lesion or a slow-growing glioma, but could not differentiate between them.

Radionuclide scintiangiography of the spinal cord is a valuable diagnostic alternative in the evaluation of a vascular cord lesion as noted by Fazio, et al. (1969) and DiChiro, et al. (1973).

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Southern Minnesota Medical Association Annual Meeting

Sheraton Airport Inn, Bloomington, Minnesota — September 14-15, 1979

Program

10:00 AM Carcinoma of the Breast
Treatment of Carcinoma of the Breast — A 20 Year Experience in Private Practice — Donald W. Hannon, M.D., St. Paul.
Chemotherapy for Breast Cancer — Current Recommendations — William A. O'Brien, M.D., Minneapolis
11:00 AM Evaluation and Treatment of Soft Tissue Knee Injuries
Physical Diagnostic and Radiologic Evaluation of the Injured Knee — Arnold L. Hamel, M.D., Minneapolis
Arthroscopic Surgery of the Knee — Kenath H. Sponsel, M.D., Minneapolis
Restoration of the Injured Knee — Rick Cunningham, A.T.,C., Minneapolis
12 Noon Annual Business Meeting and Luncheon
1:30 PM Thoracic Diseases
Running and Coronary Risk Factor Reduction — Richard L. Reese, M.D., Minneapolis
New Techniques in the Performance of Coronary Artery Bypass Surgery — Richard C. Lillihei, M.D., Minneapolis
Technical Details for Repair of Pectus Deformities — Aydin Bilgutay, M.D., Minneapolis
2:40 PM Computerized Body Scanning — Indications and Limitations — — Robert R. Foley, M.D., Minneapolis
3:40 PM Evaluation and Management of Problem Pleural Effusions
Newer Diagnostic Modalities in the Evaluation of Pleural Effusions — J. A. Meadows, M.D., Rochester
Long Term Follow-Up of Patients with Non-Diagnostic Thoracotomy for Pleural Effusion — A Series Report — Norman Hepper, M.D., Rochester
Management of Malignant Pleural Effusions — Douglas T. Coles, M.D., Rochester

Saturday — September 15, 1979

9:00 Gallstone Disease
Cholecystectomy in a 35-Bed Hospital —Mansur Taufic, M.D., Austin
Medical Dissolution of Gallstones-Present Status and Future Prospects — Harry H. Hoffman, M.D. Rochester
New Aspects of Biliary Radiology-Diagnostic and Therapeutic — Robert L. MacCarty, Rochester
10:00 AM Peripheral Vascular Problems of the Lower Extremities
Current Trends in the Management of Varicose Veins — Karl A. Lofgren, M.D., Rochester
The Role of the Vascular Laboratory in the Evaluation of Arterial Disease — Philip J. Osmundson, M.D., Rochester
False Aneurysm of the Left Ventricle — A Case Report — William D. Kelly, M.D., Minneapolis

The Southern Minnesota Medical Association gives you the opportunity to obtain 7 hours of Category I credit. The only cost is your Annual Membership dues. Non Members are also invited to take advantage of this opportunity as guests of the Society.

As an organization accredited for continuing medical education, the Minnesota Medical Association verifies that these continuing medical education activities meet the criteria for Category I on an hour-for-hour basis for the Physicians' Recognition Award of the American Medical Association.

A reminder

ZYLOPRIM®

(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout,
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age: Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

Complete information available from your local B. W. Co. Representative or from Professional Services Department PML.

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Diagnosis of Acute Knee Injuries

JAMES D. PRIEST, M.D.*

Knee injuries are common and may be confusing to the examining physician. Accurate diagnosis is often possible through history, examination, Xrays, and aspiration. Arthrography and arthroscopy are specialized techniques when the diagnosis is still in doubt.

THE KNEE JOINT of man was not designed to withstand many of the stresses applied to it in modern recreational activities. Unlike a ball-and-socket joint where movement is virtually free in all directions, the knee is a condyloid joint[1] allowing free flexion and extension, modest rotation, and almost no medial or lateral bending. The joint surfaces of the femur, tibia, and patella, are covered by a layer of hyaline cartilage, and the two shock-absorbing menisci, also cartilage, lie medially and laterally on the tibia. The joint is held together by four major ligaments and a tough capsule which thickens in some areas to form other ligaments. When inordinate stresses are placed upon the knee, whether in sports, recreation, or occupation, one or more of these structures may be damaged. This paper will outline for the primary physician diagnostic techniques in evaluation of the injured knee.

History, examination, routine Xrays, and aspiration of the knee are diagnostic procedures available in the physician's office, and this paper will dwell mainly on these. Arthrography is an Xray examination, with a radio-opaque dye, or the dye together with air, injected directly into the knee joint. It is particularly useful in diagnosing tears of the menisci. Otherwise radiolucent, the menisci are outlined by the dye; when present, a tear is demonstrated by dye within the meniscus. Arthroscopy is a surgical technique allowing visualization of the inside of the knee joint with an endoscope. This technique will be discussed in a second paper in an upcoming issue of MINNESOTA MEDICINE.

History of Injury

A simple history of the knee injury itself can be of great value in diagnosing internal derangement. A twisting injury, such as might occur when an athlete plants his foot and changes direction, may cause one of the two menisci to tear. Hyperflexion of the knee may cause a lateral menisci tear. A forceful blow from the side, as in a football tackle, is classic in causing ligaments to tear. A forceful blow from the front, as when the knee strikes the dashboard, can cause damage to the joint side of the patella.

A history of the knee buckling or giving way is classic for a meniscus tear, but also may be produced by a loose body, ligamentous laxity, or patellar abnormalities. A history of the knee locking in a flexed position, with the patient unable to straighten it, is common with meniscus tears, but also may be caused by loose bodies and osteochondritis dissecans. Pain when sitting in one position for a long time, and pain on going up and down stairs, is common with cartilage damage to the joint side of the patella. It is important to elicit the location and duration of symptoms. Finally, it should be remembered that pain sensed in the knee may be referred from the hip.

Examination of the Injured Knee

To follow is a description of the basic knee examination. The examination is often easier to perform a week post-injury, because the initial pain and swelling may make the definitive diagnosis difficult if not impossible to ascertain. If ligament laxity is not discernible, and if infection is not present, which two conditions should be considered relative emergencies, nothing is lost by placing the knee at rest for a few days before re-examination. One may find that a knee, which was widely painful and tender when initially seen, has an isolated area of discomfort several days later.

Swelling

Any swelling in a knee is abnormal. It may be secondary to rheumatoid arthritis, gout, or infection, or it may be a traumatic bloody effusion, but whatever the cause may be, it is abnormal. The normal knee has

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This is the first of two articles by Dr. James Priest on the diagnosis of knee disorders. The second will be published in MINNESOTA MEDICINE next month.

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no externally visible or palpable fluid, and contains only enough joint fluid to lubricate the cartilage surface. Most effusions are easily seen when compared with the opposite knee, but with a small effusion, it may be necessary for the examiner to sweep his hand downward over the suprapatellar pouch, milking the fluid distally, to then be able to note a small amount of fluid on one side of the patella or the other, at the joint line. The patella may also be ballotable with a small effusion.

Range of Motion

Flexion and extension should be full in a normal knee. These should be compared with the opposite knee, but normally would be from full extension (or several degrees of hyperextension) to 130 to 140 degrees of flexion. Lack of full extension might be caused by a torn cartilage, osteochondritis dissecans, or a tense effusion. Pain on flexion might be secondary to ligamentous injury or damage to the posterior portion of a meniscus.

Tenderness

Tenderness is an important sign in evaluating knee injuries. Tenderness directly over a medial or lateral joint line is perhaps the most important sign in diagnosing a torn meniscus. Tenderness over the medial femoral epicondyle or the medial tibial condyle usually indicates that a medial collateral ligament injury has occurred. Tenderness over the medial or lateral edge of the patella usually signifies that patellar abnormality or injury is present. The quadriceps mechanism inserts into the tibial tubercle, and in a growing child tenderness directly over this point could indicate Osgood-Schlatter's disease.

Ligament Laxity

Ligaments run from bone to bone, and are of utmost importance in maintaining the stability of a joint. The medial and lateral collateral ligaments, and the anterior and posterior cruciate ligaments, all run between the tibia and femur. They allow free flexion and extension of the knee while controlling anterior and posterior translation of the tibia on the femur. When torn, ligaments tend to heal in a more relaxed or elongated state than prior to injury, allowing abnormal motion of one bone on another. Unexpected movement of the tibia on the femur may cause sudden, painful buckling of the knee joint, and lead in time to damage to articular cartilage and the two menisci. A common triad of injuries was described by O'Donoghue[2] to include tearing of the medial collateral and anterior cruciate ligaments and of the medial meniscus.

Ruptured ligaments are common, and severely ruptured ligaments are probably the most disabling of all injuries to the knee. When knee ligaments are found to be lax, surgical repair should be undertaken no later than two weeks after injury, and more ideally within one week. For this reason, the patient with acute knee ligament rupture should be referred to a surgeon without delay.

Very recently, separate investigators have found a high correlation between a traumatic bloody effusion and a tear of the anterior cruciate ligament.[3] In fact, these investigators have noted the anterior cruciate ligament to be torn in about 70 percent of acute bloody effusions of the knee. In addition, a knee with an anterior cruciate ligament tear has about a 50 percent chance of having a torn meniscus as well. If, therefore, a patient presents with a traumatic, bloody effusion in the knee, referral for possible surgery should be made.

On examination, the medial and lateral collateral ligaments should be stressed in both full extension and in 20 to 30 degrees of flexion. While stable in full extension, a collateral ligament may be found to be loose in flexion. Medial knee ligaments are tested with one of the examiner's hands exerting pressure over the lateral aspect of the knee and the other over the medial aspect of the ankle. Lateral knee ligaments are stressed in a reverse fashion with pressure over the medial knee and lateral ankle.

The anterior and posterior cruciate ligaments, which cross inside the joint, are aligned to resist abnormal forward and backward excursion of the tibia on the femur. These ligaments are tested with the knee in some flexion, and the patient's foot braced or held by the examiner so that it will not move. The leg is grasped just below the knee, and the examiner attempts to displace the tibia forward and backward. Most orthopaedic surgeons agree that abnormal forward movement of the tibia indicates rupture of the anterior cruciate ligament (as well as injury to other structures), while backward displacement signifies a posterior cruciate ligament injury. These anterior and posterior drawer tests are performed with the foot pointing straight ahead. When the foot is externally or internally rotated, and the drawer tests are repeated, rotational instability may be detected. Medial and lateral rotational instabilities have been recognized in recent years to cause knee disability, often severe. This type of instability is felt to result from rupture of several structures in the knee. When diagnosed, it should be treated as any other knee ligament injury, even with early surgical repair if indicated.

McMurray's Sign

McMurray's sign is a click or clunk discernible over the medial or lateral joint line on flexion and extension of the knee and on twisting of the leg.[4] A positive sign may indicate that a torn meniscus is present. It is probably not as accurate a finding as tenderness directly over the joint line, but may be a help in diagnosis.

Patellar Signs

The patella is recognized as the source of many knee problems. The patella can fully dislocate, partially dislocate (sublux), incur articular damage on its joint surface (chondromalacia), or simply cause pain (patello-femoral pain syndrome). The patient often describes the pain associated with the patellar abnormality as occurring in the front of the knee or directly on the undersurface of the kneecap. Patellar problems are now known to cause buckling, locking, pain, and swelling of the knee. Discomfort about the patella, however, may not begin until several months or even years after injury such as a blow over the front of the knee.

Patellar problems are often elusive and examination may be vital to their discovery. The patella is examined with the knee fully extended. When, in daily life, a patella subluxes or dislocates, it moves laterally, not medially. To diagnose this abnormality, a lateral deviation or apprehension test is performed with the examiner forcefully deviating the patella to the lateral side. A patient whose kneecap subluxes or dislocates may become greatly apprehensive with this maneuver. Tenderness under the medial or lateral edge of the patella may indicate either damage to the joint side of the kneecap or patello-femoral pain syndrome. Possibly the most sensitive test for patellar problems, and the one often positive when others are negative, is compression by the examiner over the superior aspect of the patella. Especially when the patient accompanies this compression with contraction of the quadriceps muscle, this test may elicit the elusive discomfort he or she suffers.

Aspiration of the Knee

Aspiration of the knee under sterile conditions should be considered if a large, painful effusion is present, merely to relieve intra-articular pressure, or if, after the history and physical examination, a diagnostic dilemma persists. Aspiration may be best accomplished by entering the joint with a large bore needle (16 or 18 guage) in the superolateral aspect. If a bloody effusion is found, it may be drained for the comfort of the patient, but may also recur. Fat droplets in the blood may signify the presence of an intra-articular fracture. An acute bloody effusion is usually traumatic, indicating that something in the knee has been torn, but it may occasionally indicate the presence of a coagulopathy such as hemophilia. When there is suspicion that the effusion is non-traumatic, the fluid may be sent to the laboratory for analysis. If one remembers to request the "three Cs" (cell count, crystals, and culture), many of the common causes for joint effusion can be ruled out. An elevated cell count could indicate infection, as would be a positive culture. Gout or pseudogout might be diagnosed by the presence of crystals.

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MINNESOTA MEDICINE

The Board of Editors of MINNESOTA MEDICINE invites the members of the Minnesota Medical Association to submit examples of their art work for publication on the cover of MINNESOTA MEDICINE. Color photographs, preferably transparencies, as well as photographs of paintings, drawings, sculpture, ceramics, jewelry, etc., are all welcome. There is no limit as to subject, but pictures of Minnesota or subjects topical to a month or season may have a slight advantage. Pictures will be returned if identified with the name and address of the maker. Please submit pictures to the Editor of MINNESOTA MEDICINE, 101 East 5th St., Suite 900, St. Paul, Minnesota 55101.

Case Report

Tracheal Cylindroma

Report of a Case with External Tracheal Prosthesis

RICHARD C. WOELLNER, M.D.* and ALAN C. HYMES, M.D.†

A case is presented of a large tracheal adenoid cystic carcinoma (cylindroma) which was treated by extensive tracheal resection and radiation. A tracheal prosthesis was made connecting the patient's larynx and thoracic tracheal stoma. This prosthesis was worn externally and could be removed and re-inserted easily by the patient. Some problems of treatment of tracheal tumors are discussed. Earlier diagnosis of a tracheal tumor may be helped by understanding some of the physiology of tracheal obstruction.

TUMORS OF THE trachea occur rarely, but present a life threatening situation because of their location. They are difficult to see on standard Xray and history or physical examination must provide more help than in other intrathoracic neoplasms.

Even though it functions as a more or less inert tube, the trachea is sorely missed after it is removed, and surgical replacement procedures have been difficult. We present an interesting case of a large tracheal tumor treated with resection and an *external* tracheal prosthesis which functioned up to the time of the patient's death from recurrent tumor over six years later.

Case Report

The patient was a 43-year-old woman who was seen initially in February 1970 because of episodes of wheezing. She had had hay fever for many years and in the distant past had had some "asthma." Approximately six months before the first admission, her dyspnea recurred and increased. She was treated with bronchodilators without effect. She had smoked lightly only from age 20 to 22 years.

Physical examination of her chest showed normal air flow peripherally but a central inspiratory high-pitched single wheeze. Chest Xray was normal. Lateral and oblique planograms revealed a lesion in the upper trachea obstructing approximately ninety percent of the lumen (Figure 1). Indirect laryngoscopy was normal. It was elected not to bronchoscope her because of fear of edema and further obstruction.

Because of the extent of the tumor visualized on planigraphy, a combined antero-lateral right thoracotomy with a right sided neck incision was performed This revealed a tumor mass within the trachea extending from just below the larynx. An initial segment of the trachea, measuring approximately 5.5 cm in length, was removed. At the time of resection, a second sterile endotracheal tube was put into the distal tracheal stump within the thoracotomy wound. The distal tracheal stump was brought out to the chest wall in the right third intercostal space. In order to do this, the right and left main stem bronchi were mobilized to the lower lobes. A Penrose drain was placed under the crotch of the carina, and the trachea was brought out between the superior vena cava and the aorta, as it would have obstructed the superior vena cava had it been brought out more laterally. A window was made in the right third intercostal space by partial removal of the third and fourth costal cartilage. Frozen section of the trachea showed submucosal spread of the cylindroma. Because of the proximity of the carina no further distal resection was done. The tracheal stoma below the larynx was closed.

Her postoperative course was complicated by tracheitis, bronchitis, atelectasis, and pneumonitis, partly as a consequence of a tendency of the tracheal stoma to retract. Within two weeks the

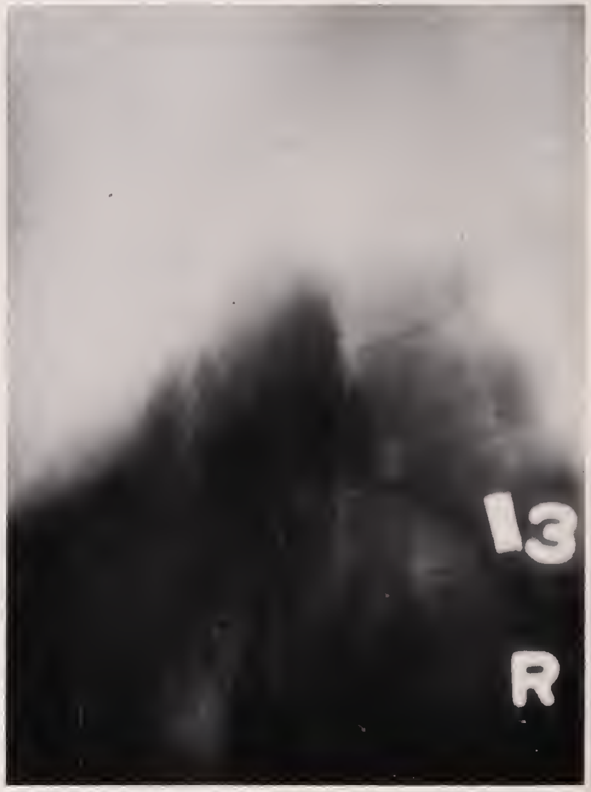

Fig. 1 — Lateral planigram showing tracheal mass.

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stoma was revised removing more cartilage and suturing the skin directly to the tracheal stoma by mobilizing skin flaps. Because of tumor involvement of the distal tracheal stump, the patient was given local radiation therapy.

Since she still had her larynx it seemed reasonable to connect the remaining ends of the trachea with an external plastic prosthesis. Six weeks following radiation, the proximal tracheal stump was re-opened and brought out to the skin as a proximal end on tracheostomy (Figure 2). The two stomas were then connected with a removable prosthesis fashioned by molding plastic tubes to fit the stomas and connecting them with a plastic tube (Figure 2).

Following several readjustments of the cuff fittings, crusting and infection problems with the distal stoma cleared and by July 1970 the patient was doing extremely well with no further respiratory infections. Her strength returned to nearly normal, and by September 1970 she was able to speak quite well and had an acceptable soft speaking voice. She did well until November 1972 at which time she developed a small raised white lesion by the distal stoma, which was biopsied and found to be benign.

In March 1973 she was found to have some small nodules in the left mid-lung field on Xray, and had another thoracotomy with the finding of multiple small recurrent tumor nodules. Postoperatively she was begun on treatment with Cytoxan and Methotrexate. She remained asymptomatic, and in February 1974 Vincristin was added to the above regimen. By September 1974 she had developed recurrent respiratory infections, and by April 1975, chest Xray showed continued progression of the thoracic metastases. She continued to feel well until August 1975 at which time she developed weight loss and increasing cough and secretions from the lower tracheal stoma. She was started on Adriamycin and CCNU without great improvement, and Bleomycin was added to her regimen in January 1976. By April 1976, she was able to be moderately active and to travel. Following that, however, she developed progressive weakness and fever and expired at home in September 1976, 6 years and 7 months following her initial tracheal resection.

Discussion

The initial impression that this patient was asthmatic is a common mistake in this condition. Young adults rarely develop non-asthmatic wheezing, but in this patient the location of the tumor presented a clue which suggested the site of obstruction.[1] and the tumor was further localized by planigraphy.

The trachea is not rigid and responds to the pressure of surrounding tissues. During forced expiration, with a higher intra-thoracic pressure, the trachea will tend to collapse within the thorax. Above the sternal notch, however, the surrounding tissue pressure is less, and the trachea will expand during expiration. These pressure relationships are reversed during inspiration: the intra-thoracic trachea will tend to expand and the extra-thoracic trachea to collapse. If it is partly occluded, this collapse may produce an audible wheeze, whose timing in the respiratory cycle will depend upon its location.

Miller and Hyatt[2] analyzed flow volume loops of various types of tracheal obstruction. They found three types: fixed inspiratory and expiratory resistance, as with a hard fibrous stricture; inspiratory obstruction, with extrathoracic tracheal lesions; and expiratory obstruction, with intrathoracic lesions. Our patient had striking inspiratory obstruction, accentuated by the fact that her tumor was soft and that by invading the tracheal wall it probably decreased its rigidity. Her tumor was located primarily in the cervical trachea, and her inspiratory stridor thus provided a clue to its location.

Special Xrays of the trachea generally are needed to visualize these intraluminal tumors. Oblique films and lateral or oblique planigrams may be needed to show the outline. The intraluminal lesion should be visualized easily with rigid or flexible bronchoscopy. However, since the lumen of the trachea is very narrow by the time most of these tumors are detected, bronchoscopy easily could cause complete airway obstruction. Additionally, these tumors are very vascular and biopsy frequently produces severe hemorrhage. For these reasons, patient and staff should be ready for definitive surgery before biopsy is attempted.

Tracheal tumors may present with airway obstruc-

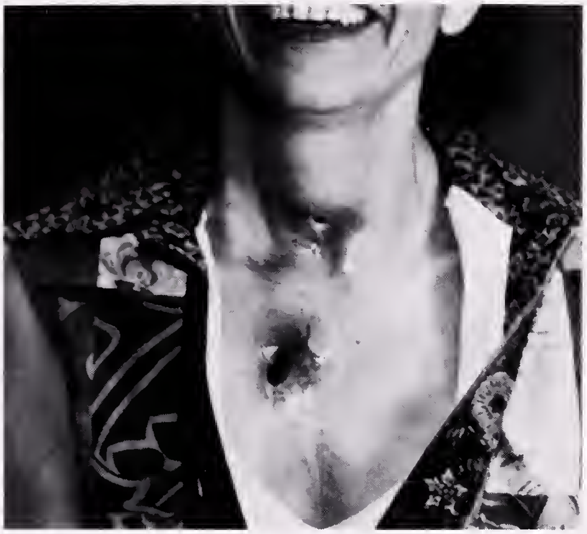

Fig. 2 — Patient, showing laryngeal and tracheal stomas.

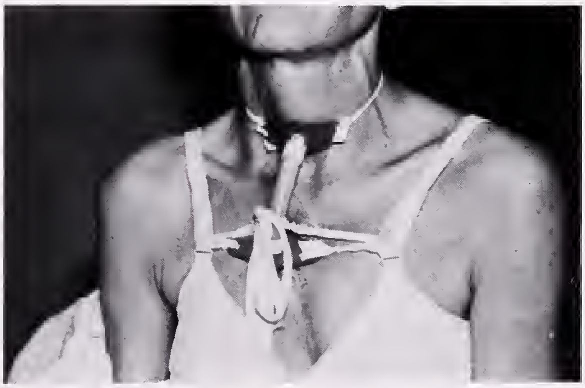

Fig. 3 — Patient with tracheal prosthesis in place.

tion, as in this patient, or with hemoptysis. Primary tracheal tumors are extremely rare. Over half[3,4] of these are squamous cell, and another one-third are adenocystic carcinomas, or "cylindromas." Interestingly, although 85 percent[5] of bronchial adenomas are of the carcinoid type, these are rarely found in the trachea. Cylindromas typically grow very slowly, but are persistently and deeply invasive and tend to recur. They have a low but definite potential to metastasize, and repeated biopsies of the tumor occasionally will show that its microscopic appearance tends to become less differentiated as the years go by.[3] Long survivals seem to be common, and since much of the tracheal lumen must be obstructed before symptoms develop, it is likely that the tumors are present for years before they are detected. The tumors are quite vascular, and the overlying mucosa may rupture intermittently, causing hemoptysis. Adenocystic carcinomas are not particularly radiosensitive[4] but some palliative effect may be obtained with radiation. Surgery, with complete tracheal resection, is the treatment of choice, although the extensive local invasiveness and undermining characteristic of the tumor tend to decrease the cure rate from this form of therapy also.

Surgical treatment of invasive tracheal tumor implies extensive resection of the trachea. If more than 4.5-6 cm of the trachea is removed, it is impossible to re-anastomose the structure[6] and either low tracheotomy or tracheal replacement must be performed. The former produces major problems due to the fact that the filtering, humidifying, and warming functions of the upper airway are bypassed, and the lower tract becomes susceptible to crusting and infection. In addition, the function of the larynx in speech and coughing is lost. Implanted tracheal prostheses of many types have been used, formed of both grafts and synthetic material.[5] They all have common problems of leakage, infection, and stricture formation. Wycherlis and Neville[6] have reviewed the literature on implanted prosthesis and tracheal reconstruction procedures. A procedure similar to that used in our patient was performed by Lawrence et al,[7] with satisfactory insertion and function of an external removable tracheal prosthesis.

In our patient, because of the problems inherent in implanted prostheses and because of the short remaining length of trachea above the carina, it was elected to leave her parasternal tracheotomy in place and to create another tracheotomy beneath the larynx, connecting the two with a removable external prosthesis. As noted in the case summary, this prosthesis worked extremely well for the duration of her life. She was able to speak well with an adequate voice volume, could cough and raise secretions, and had no evident dyspnea. She wore high-necked clothes which concealed her prosthesis, and before she developed tumor recurrence led a reasonably normal life for five years.

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Cover Photograph
"Autumn in Wisconsin"

Dr. Richard N. Hadley, an orthopedic surgeon with the Nicollet Clinic in Minneapolis, took the cover photograph at Hayman Falls County Park in Shawano County, Wisconsin. The water is the Embarrass River which is contained by an old abandoned hydroelectric generating plant.

Dr. Hadley has been in Minneapolis for two years and took his residency in Wisconsin. It was during this time that he took the cover photograph.

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†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Brief Summary

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CDNTRAINDICATIONS. Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis; toxic megacolon complicating ulcerative colitis; myasthenia gravis. WARNINGS In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIDNS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy Use with caution in patients with: Autonomic neuropathy. Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension. Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIDNS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these. Adverse reactions may include xerostomia; urinary hesitancy and retention; blurred vision and tachycardia; palpitations; mydriasis; cycloplegia; increased ocular tension; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia, nausea, vomiting, impotence; suppression of lactation; constipation, bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating. With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DDSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs.

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Letters to the Editor

Dear Editors:

Senior Citizen Retired Physician

I have read Dr. Rice's Emeritus Editor's Soliloquy,* and as a "Senior Citizen Retired Physician" I understand his concern and share his distress. Fortunately, as a member of the Minnesota Board of Medical Examiners I can assure him the Board does not revoke, suspend or limit the license of retired physicians. It treats the "Senior Citizen Retired Physician" in exactly the same way it treats any other licensed physician. If a licensed physician does not fulfill the re-registration requirements, the license is not renewed, and he or she cannot practice medicine in Minnesota until the license registration requirements have been met and a valid license issued.

To fulfill the re-registration requirements, the registration form must be completed, the registration fee paid, and evidence presented of having completed 150 hours of approved Continuing Medical Education during the previous three year period. If the physician fails to fulfill the above the license simply is not renewed, and obviously he does not hold a valid legally usable license to practice medicine. The license can be renewed at any time, even years later, by simply paying the back registration dues and presenting evidence of 150 hours of Continuing Medical Education having been obtained during the immediate past three year period.

Minnesota, at this time, has no Emeritus Status for physicians. Such a status really would seem to serve no purpose and actually might be limiting in character. At present if the physician elects not to re-register, he or she does nothing and then has a dormant license. Obviously, the physician cannot legally practice medicine of any type but has the option to make the license valid at any time by fulfilling the above requirements and re-registering.

We "Senior Citizen Retired Physicians" who wish to practice part time or "occasionally write a prescription" are just as subject to the above laws, but no more so than any other licensed physician. The CME requirements are a burdensome chore, and yet they are required by our state. These CME requirements were approved by the Minnesota Legislature with the best of intentions. The hope is that this CME will encourage Minnesota Licensed Physicians to stay more current in medical knowledge and practice even more competent medicine. The need for some method to try to assure competence is even more pertinent in the case of the physician who "occasionally practices," than for the full time physician. The Minnesota Board of Medical Examiners has as its major charge the protection of the health of the citizens of our state. It is absurd to argue that CME does not have the potential for keeping the physician current in the much needed knowledge of the practice of medicine.

The rules relating to Continuing Medical Education (7MCAR g 4,012) state: "the Board may refuse to renew, suspend, condition, limit or qualify the license of any persons whom the Board determines has failed to comply with the requirements of this rule." This does not speak of revoking the license. Revocation occurs only after a formal hearing before the entire Board, and this is not pertinent to the above rule.

I hope this helps to explain the rules relative to CME.

J. C. Cain, M.D.
Minnesota Board of Medical Examiners

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*Minnesota Medicine 62:3:188, March, 1979.

Dear Editor:

U.S. Health Care System

I continue to enjoy reading MINNESOTA MEDICINE and the editor's notebook in particular. Your article in the April 1979 issue was particularly thought provoking.

I wish I could share your optimism about what will happen to medicine and the U.S. Health Care System in the next ten years. Let me take a few of the points that you have covered and tell you why I am skeptical. Parenthetically, it is somewhat humorous that you who are more closely identified with the private sector are optimistic, while I, although in a state university and therefore conceivably more identified with the public sector in medical care, am more skeptical.

The first area which you commented on was the prospect for national health insurance. The options in this area are going to be influenced radically by the next election. Certain political figures are dependent for their political base on the support of large groups such as the unions. To command that support, they will clearly have to call for a comprehensive national health insurance bill. Other politicians whose base comes from business, will seek a more limited kind of bill which would include the one you described, mainly a catastrophic bill. Very few people were able to predict in 1975 that Jimmy Carter would be president; I am no better able to predict now who will be president in 1980. Given the severe impact that inflation is having on the working man, labor will have to take a strong position in the forthcoming election. Thus, we may have a president who will have committed himself to comprehensive national health insurance in order to gain labor support. This reflects the feelings of some that the only way to control health care costs is to have national health insurance. I doubt that it will be effective in this regard.

You cite opinions of several people who are less than enthusiastic about a national health insurance bill. Basically these people are of the conviction that whatever our problems are in the current health care system and wherever the present menage à trois of private, federal and state control has failed, simply imposing more federal control will not solve the problem. One does not have to go far to quote an equal number of persons who are of exactly the opposite conviction, namely that because our present level of control has failed, what we need is more control. Senator Kennedy is certainly one of these. You note that Enthoven dismisses the Kennedy health security program as managerially impractical. Although his statement may be true, it will not necessarily prevent the program coming to pass if it is able to generate significant political support. Further, many people who have mixed feelings about a comprehensive bill are afraid to oppose it for fear that they will be seen as opposing what would be reviewed as a motherhood issue.

I think that Drucker's prediction that more and more health care delivery will tend to be "organized", that is, to be arranged through groups and other institutional forms of medical care is true. It is no less true that private practice will not disappear in the next ten years. Another issue that is important to take into consideration is the effect of continued escalation of health care costs. Whether these costs are appropriate or not, the public has come to believe, and many legislators believe, that this growth in cost must be curtailed to a maximum of 9% annually or less. If physicians, hospitals and health insurance plans cannot bring this control about in the next 3 to 4 years, the pressure will be intense to introduce a form of government intervention that will cure this apparently incurable disease. The fact that Medicare itself has contributed to this escalation of costs will not daunt many of those who are of the philosophical conviction that the government needs to be in greater control.

In closing, I would point out two particularly disturbing features about the government role in health care. First, the Veteran's Administration Hospital System is, I believe, the largest single health care subsystem in the United States. While it may well provide a number of valuable and important services to veterans, and while there are individual centers of excellence, I am singularly unimpressed that it is a model system or that it represents the kind of health care that would be acceptable to the majority of people in this country. Most importantly, it should be noted that the control of costs in the VA system has either been sporadic or has been only achieved at the expense of program curtailment. As you are well aware, the capital expenditures of the VA hospital system are not subject to HSA review.

I would like to share your optimism, but there is very little on the horizon that leads me to feel hopeful. I do believe that all physicians must continue to work to improve the quality, availability, effectiveness and cost control of health care and until definitive actions are taken by the Congress, there is always a chance to avoid it. I shall keep your article and a copy of my letter, so that we can compare notes in 10 years. If you are right (and we are both still here), I will be happy to make a $100.00 contribution to Minnesota Medicine or some other worthwhile activity of your choice. Of course, given the current inflation, that may not amount to very much.

William J. Klein, Jr., M.D., F.A.C.P.*
East Lansing, Michigan

P.S. — Although my letter arrives after Senator Kennedy's big barrage on National Health Insurance and the assembling of his support committee, it was written beforehand.

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*Director, Office of Health Services, Professor of Medicine and of Community Health Science, East Lansing, Michigan.

Uremic Pericarditis

Dear Editor:

I read with interest the article SURGICAL TREATMENT OF UREMIC PERICARDITIS which appeared in *Minnesota Medicine,* May, 1979.[1] The authors have had an excellent track record utilizing the surgical approach and their long-standing expertise in the field of uremic pericarditis is unquestioned. I would however like to point out some of the advantages of transcutaneous instillation of triamcinolone hexacetonide into the pericardial space as a relatively non-invasive (requiring no surgery) approach to the problem of intractable pericardial effusion.

Although I am now limiting my practice to dermatology, during the seven years prior to my dermatology fellowship I had experience with numerous cases of intractable pericardial effusion while serving as associate director of hemodialysis, Departments of Medicine and Surgery, University of Minnesota Hospital.

We treated 46 effusions in 45 patients. In general, patients who did not respond to systemic steroids, increased dialysis durations, and Indocin had the percutaneous placement of an intrapericardial catheter with subsequent infusion of the relatively nonabsorbable steroid triamcinolone hexacetonide (Aristospan). Forty-four of these patients had no recurrences during one to fifty-four months of follow-up. One patient had a recurrence six months after triamcinolone instillation. One patient required pericardiectomy after catheter placement had been unsuccessful due to loculated and adhesive compartment formation. The only complication was that of an asymptomatic internal mammary artery fistula which if counted as a major complication would represent a two percent complication rate which compares quite favorably to the variably reported complication incidence of either pericardiectomy or systemic steroids.

We felt this method was desirable as it represented one of the world's largest experiences with intractable uremic pericardial effusion, offers almost universally effective therapy with a minor complication rate compared to those associated with the inconvenient, if not dangerous, pericardial fenestration or pericardiectomy.[2]

It is not my intent to discredit any of the statements made in the article referenced but only to offer our experience and an alternative effective mode of therapy where intrathoracic surgery is not desirable.

T. J. Buselmeier, M.D., F.A.C.P.
Minneapolis, Minnesota

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*Associate Professor of Medicine and Surgery, University of Minnesota Hospitals. Univ. of Minn. Hospitals, Minneapolis, Minnesota.

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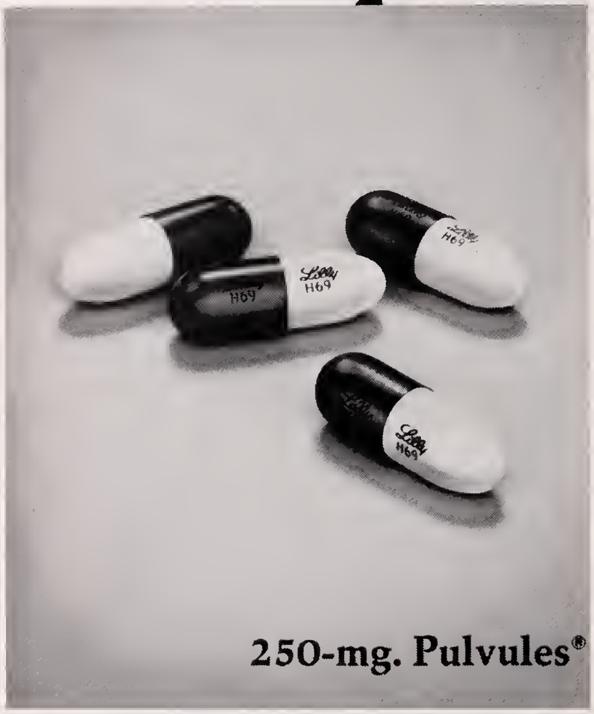

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Testicular Surprises in Two Apparently Healthy Young Men

MILES J. JONES, M.D.† and GENE P. SIEGAL, M.D.*

Autopsy findings are presented from two cases of apparently healthy young men with abnormal testes. The testicular lesions are described and implications with regards to infertility, diagnosis, and etiology of Klinefelter's and Sertoli-Cell-Only syndromes are presented. A plea is made for careful testicular examination at the time of necropsy.

DETAILED EXAMINATION of the testes is often neglected in asymptomatic individuals in clinical practice and at the autopsy table. Two autopsies were recently performed in which unsuspected lesions of the testes were identified.

Case Reports

Case 1

A 23-year-old white male had died from carbon monoxide poisoning. No additional pertinent medical history was obtainable. No grossly pathologic lesions, except slight splenomegaly and scattered petechial hemorrhages on pleural surfaces were found. The color and consistency of the testes were normal, but they were small; the larger measures 1.2 x 1 x 0.9 cm.

Case 2

A 29-year-old white male had also died from motor vehicle related carbon monoxide poisoning. His blood ethanol level was 515 μg/ml. He was married twice, but had no children. There was no other relevant medical history. At necropsy hepatomegaly (weight 2445 gm) secondary to acute and chronic alcoholic liver disease, acute pulmonary edema, and moderate visceral congestion were identified. The testes had normal size, color and consistency. The larger measured 4.9 x 3.5 x 1.9 cm.

Microscopic Description and Diagnoses

Case 1

The testes showed striking Leydig cell hyperplasia. Some tubules were totally hyalinized, others showed atrophy of the Sertoli cells and thickening of the tunica propria, no spermatogenic activity was observed (Figure 1). Diagnosis: Klinefelter's syndrome (sclerosing tubular degeneration).

Case 2

The testes showed no spermatogenic activity. The number of tubules was normal, but their diameter was decreased and most contained no germ cells. The Sertoli cells were abundant and were aligned vertically to the basement membrane of the tubules. Some of

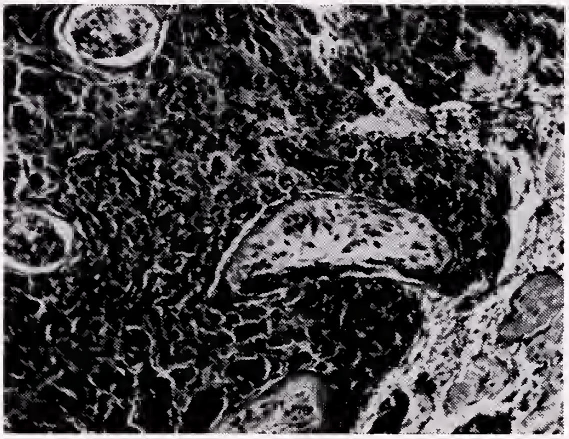

Fig. 1 — Large polygonal eosinophilic Leydig cells surround degenerating seminiferous tubules. Tubules containing Sertoli cells are decreased in size and number. The tunica propria is thickened. In the lower right corner two hyalinized seminiferous tubules can be seen. (H&E 160x).

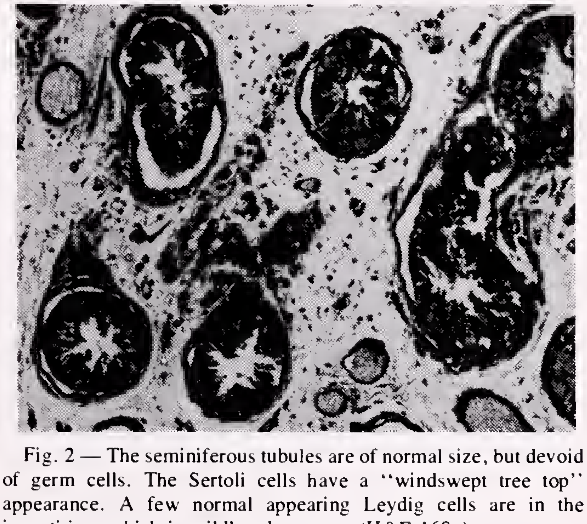

Fig. 2 — The seminiferous tubules are of normal size, but devoid of germ cells. The Sertoli cells have a "windswept tree top" appearance. A few normal appearing Leydig cells are in the interstitium which is mildly edematous. (H&E 160x)

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Reprint Address: Dr. M. J. Jones, Department of Pathology and Anatomy, Mayo Clinic/Foundation, Rochester, Minnesota 55901.

the Sertoli cells resembled "windswept tree tops." The Leydig cells appeared normal; but there was mild interstitial edema. A rare tubule had a few germ cells, which had not developed past the secondary spermatocyte stage (Figure 2). Diagnosis: Sertoli-Cell-Only syndrome (absence of germ cells).

Discussion

Abnormal testes were found in two normal appearing young men. While it is not uncommon to find areas of decreased spermatogenesis and thickened basement membranes in normal testes, it is rare to find abnormalities of the entire testicular tissue.[1] In infertile marriages, approximately four out of 15 men will have striking testicular lesions.[2] The most common testicular lesions causing infertility are listed in the Table.

TABLE

Testicular Causes of Infertility*

Maturation arrest and hypospermatogenesis
  a. Elevated temperature
  b. Antecedent febrile illness (typhus, malaria, brucellosis, etc.)
  c. Noxious chemicals (Petroleum products, Lead fumes, Insecticides, etc.)
Sertoli-Cell-Only syndrome (absence of germ cells)
Klinefelter's syndrome (sclerosing tubular degeneration)
Cryptorchism
Irradiation damage
Mumps or Gonococcal orchitis

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*Slightly modified from Wong, et al.[6]

The incidence of Klinefelter's syndrome in the general male population is between 0.15-0.24%.[3] The classic form of Klinefelter's syndrome is characterized by small firm testes, gynecomastia, and decreased androgenic features, however, variant forms do exist. A 47 XXY pattern in a karyotype confirms the diagnosis. Klinefelter's syndrome differs from Reichstein's syndrome which has a 46 XY karyotype although it has the same phenotypic feature as Klinefelter's syndrome.[4] Early detection and treatment of the androgen deficiency are important in Klinefelter's syndrome.[5]

The testes in true Sertoli-Cell-Only syndrome are often slightly smaller than normal, but their consistency is normal; azoospermia and elevated FSH titers are present. This syndrome is relatively uncommon. It occurred in 7.9% of males in one series of testicular biopsies.[6] The only complaint in this syndrome is infertility. The cause of this disorder is unknown; exposure to ionizing radiation following birth has been suggested.[7,8] Failure of germ cells to migrate from the yolk sac endoderm into the embryonic gonads suggests another attractive but unproved theory.[9] In one report an XYY sex chromosomal pattern was detected in one of ten patients.[10] Similar histologic changes may also be caused by cryptorchism, mumps or gonococcal orchitis, and adult seminiferous tubule failure. These conditions can be morphologically distinguished from Sertoli-Cell-Only syndrome because, in addition to germ cells loss, they usually lead to thickening and hyalinization of the tunica propria and ultimately to sclerosis of the seminiferous tubules. Maturation arrest and hypospermatogenesis also mimic Sertoli-Cell-Only syndrome, but in these two conditions the germ cells are by comparison far better preserved. Treatment of Sertoli-Cell-Only syndrome cannot correct the infertility, which is permanent, and hormone replacement therapy is unnecessary.

The value of the annual physical examination and routine necropsy have recently undergone a great deal of questioning in the medical press. Although the cause of death in these cases seemed obvious (carbon monoxide poisoning) and indeed was confirmed by appropriate laboratory tests, failure to conduct a complete and thorough autopsy would have clearly meant failure to identify important pathology in these individuals. The suggestion that their deaths and testicular disease are related by factors other than chance has prompted both a prospective and retrospective study now underway in this department.

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Special Article

Lung Cancer Patients Treated with Corynebacterium Parvum

Phase I Toxicity Study

RICHARD YADEAU, M.D.;* HENRY A. BATES, PH.D.† and IGNACIO FORTUNY, M.D.‡

Ten lung cancer patients were given weekly intravenous infusions of Corynebacterium parvum: Five patients were on concurrent radiation, three on concurrent chemotherapy and two treated with C. parvum alone. Dosages ranged from 1.25 Mgs/m^2 to 5.0 Mgs/m^2. Major adverse side effects were fever (39°C to 41°C) chills, (moderate to severe) body aches and a transient lymphocytopenia. These toxic effects were dose dependent.

THE STIMULATORY ACTION of the gram positive anaerobic bacterium Corynebacterium parvum (C. parvum) on the reticuloendothelial system[1] and its antitumor activity in a variety of experimental animals has been described.[2]

In man C. parvum given subcutaneously or intravenously with chemotherapy has been reported to increase the survival rate of lung cancer patients.[3,4] These observations and our own interest in immunotherapy prompted us to design a patient drug tolerance (phase I toxicity) study with C. parvum given intravenously to lung cancer patients.

Materials and Methods

Patient Population

Ten patients with lung cancer were admitted into this study. Three were on concurrent chemotherapy, five on concurrent radiation and two received only C. parvum. The patient's age, sex, tumor histopathology, treatment, related clinical problems and C. parvum dosage are recorded in Table 1. Prior to program admission, the purpose and possible adverse side effects were explained in writing and verbally to the patient and attending physician. Both the patient and the attending physician were required to sign an informed consent. While on this program each patient remained under the care of the attending physician.

Preparation of Vaccines

The Prevót strain of C. parvum was cultured in our laboratory and identification of this bacterium confirmed by gas chromatography, Gram stain and anaerobic growth characteristics. The vaccine consisted of heat-formalin killed C. parvum suspended in 100 ml. of sterile physiological saline. Each individual vaccine was tested before and after each infusion for viable C. parvum and microbial contamination by standard microbiology methods.[5] Vaccines with viable C. parvum or microbial contamination were not used.

Infusion of Patients

All patients were randomly assigned to one of the following test groups of C. parvum: 1.25 Mgs/m^2, 2.5 Mgs/m^2 or 5.0 Mgs/m^2. When possible, patients received eight consecutive weekly infusions of one of the described doses of C. parvum. Patients on radiation were infused with C. parvum in the morning followed by radiation on the same day. Chemotherapy programs were designed so that C. parvum was cycled into the program at a time when the patient was not treated and when hemological parameters described below were normal. Because hemological values were frequently abnormal in patients on chemotherapy, the completion of the eight infusions usually was extended over 12 to 14 weeks. When a patient's WBC was less than 3,000 mm^2 or platelets less than 100,000 mm^2, an infusion was not given. Infusion time varied from 15 to 30 minutes with a 30 minute to three hour postinfusion observation period. Onehalf of these patients received C. parvum in the hospital and the other half on an outpatient basis. Patient's blood pressure, oral temperature and pulse were monitored at the beginning, midpoint and end of each infusion and at additional times if necessary. The infusion adverse side effects are recorded in Table 2. Outpatients were advised as to what adverse side effects could occur and asked to report to the project nurse such effects within 24 hours after each infusion.

---

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Reprint Requests To: Henry A. Bates, Ph.D., Research Department, Metropolitan Medical Center, 900 South Eighth Street, Minneapolis, Minnesota 55404.

Laboratory Tests

Renal functions were evaluated by serum BUN, creatinine and a complete urinalysis. Liver functions were accessed by serum total bilirubin, alkaline phosphatase, LDH, SGOT, albumin and total protein. Bone marrow functions and peripheral blood values were accessed by hemoglobin, hematocrit, WBC with differentials, platelets and absolute lymphocyte counts. These tests were done on each patient before, midpoint and after completion of the infusions. When indicated or requested by the attending physician additional laboratory tests were done. Abnormal results obtained during this study were reported immediately to the attending physician.

Results and Discussion

Results of our C. parvum toxicity study in lung cancer patients are summarized in Table 2. Increased oral temperature (39° to 41°C) and chills (moderate to

TABLE 1

Patient Clinical Data

Age (yrs)	Sex	Histopathology	TNM Staging*	Treatment	Other Clinical Problems	C. parvum Mgs/m²
65	F	Adenocarcinoma Stage III	$T_3N_0M_0$	Chemotherapy	None	1.25
42	F	Adenocarcinoma Stage III	$T_2N_2M_1$ Brain	Chemotherapy	None	1.25
54	M	Adenocarcinoma Stage I	$T_1N_0M_0$	Lobectomy Chemotherapy	Emphysema	2.5
60	M	Undiff. sq. cell carcinoma Stage III	$T_3T_1M_0$	Pneumonectomy Radiation	None	2.5
58	F	Large cell carcinoma Stage III	$T_3N_2M_1$	Radiation	Chronic Bronchitis	2.5
41	F	Adenocarcinoma Stage I	$T_1N_0M_0$	Thorocotomy	None	2.5
49	M	Sq. cell carcinoma Stage III	$T_2N_1M_1$	Radiation	Alcoholism	5.0
42	M	Adenocarcinoma Stage II	$T_0N_1M_1$	Lobectomy Radiation	Premature Auricular Contractions	5.0
63	F	Alveolar Cell Carcinoma Stage III	$T_2N_1M_0$	Thorocotomy	Chronic Bronchitis	5.0
63	M	Sq. cell carcinoma Stage III	$T_2N_0M_1$	Radiation	Alcoholism Artherio-sclerosis with Angina Adult Diabetes	5.0

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*Beahrs, O; Carr, TD and Rubin P (Eds). Manual for Staging of Cancer, Am Joint Comm (Chicago), 1977. (By permission)

TABLE 2

Toxic Effects of I.V.C. parvum.

Toxic Effect	# Patients Reactive	% Positive
Oral Temperature > 39°C	8/10	80
Chills — Moderate	3/10	30
Severe	3/10	30
Hypotension < 80/60 mm Hg.	1/10	10
Hypertension > 140/90 mm Hg.	2/10	20
Headaches	1/10	10
Nausea Vomiting	3/10	30
Body Aches	6/10	60
Leukocytes < 3000 mm²	3/10	30
Absolute # Lymphocytes < 1500 mm²	8/10	80
Platelets < 100,000 mm²	2/10	20
Hemoglobin — Decreased > 2 gms%	2/10	20
Renal function changes	4/10	40
Liver function changes	3/10	30

severe) were the most consistent clinical findings. These reactions began two to four hours postinfusion and persisted up to 48 hours. The severity of these reactions were dose dependent. In some cases the degree of severity was reduced after multiple infusions. Hypotension or hypertensoin were not major problems; however, the two patients who experienced hypertension during the infusions were patients with cardiovascular disease. Therefore greater caution was taken with these patients when infused with C. parvum. Body aches were reported by 60% of the patients; however, this effect was difficult to directly associate with intravenous infusions of C. parvum.

Lymphocytopenia was observed in 80% of our patients. Other investigators reported a transient lymphocytopenia in patients given C. parvum alone.[6,7] Our followup studies indicated this lymphocytopenia was a transient reaction in all but two cases. These two patients were considered to have uncontrolled disease and one expired during the course of the study. No autopsy was done. Detail studies on two patients given radiation and C. parvum and one given C. parvum alone indicated this lymphocytopenia was resolved 8 to 12 days after intravenous infusions were completed. Decreased platelets and hemoglobin were demonstrated in two patients on chemotherapy plus C. parvum. These reactions were not observed in patients on concurrent radiation or C. parvum alone. Followup studies on these two patients when they were not on chemotherapy or C. parvum showed normal values.

Prior to program admission four patients had abnormal urinalysis values which were associated with bacterial urinary tract infections. After appropriate treatment the urinary tract infections were resolved and the urinalysis values returned to normal range.

Abnormal liver functions in three patients were associated with elevated serum enzyme values (alkaline phosphatase, LDH, SGOT). These elevated serum enzyme values returned to normal in two patients 4 to 8 weeks after the completion of the C. parvum infusions. One patient with a persistently elevated alkaline phosphatase was found to have a liver metastases.

From this study we concluded that lung cancer patients generally in poor physical condition tolerated the intravenous infusions of C. parvum at the dosages used and under treatment conditions described. This tolerance study plus the inhibition of tumor growth in animals by C. parvum,[2] the reported immunological defects associated with lung cancer[8] and the availability of a suitable population of patients were factors in our decision to design a clinical study to determine C. parvum's effectiveness in increasing the survival time of lung cancer patients. A more important reason was the clinical investigations by other investigators[3,4] which demonstrated that combining C. parvum with other modalities of treatment increased the survival time of lung cancer patients.

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Minnesota Society of Clinical Pathologists

The Minnesota Society of Clinical Pathologists will hold its Annual Fall Tumor Seminar at the Minnesota Club in St. Paul on Saturday, November 10, 1979. Dr. David Dahlin of the Mayo Clinic in Rochester will be the moderator-discussant. Slides will be sent to members in advance of the meeting. Pathology residents will be guests of the Society. Nonmembers who desire information concerning the meeting may address themselves to Dr. Bill Foley, 110 E. 18th Street, Minneapolis, 55403.

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Rheumatology Corner

Nonsteroidal Anti-Inflammatory Drugs

RICHARD B. TOMPKINS, M.D.*

AS GENERALLY USED, the term nonsteroidal anti-inflammatory drugs (NSAIDs) refers to nonsteroidal, nonsalicylate anti-inflammatory drugs. Indomethacin and phenylbutazone were the first of the nonsteroidal drugs and have been available for many years. Over the last four or five years, a proliferation of newer NSAIDs has occurred beginning with ibuprofen. The most recent addition to this group is sulindac. Undoubtedly, there will be more of these in the future because others are available in Europe and still others are in the development stages.

The accompanying Table lists each of the available NSAIDs, the dosages in which they are available, the usual daily dose, and the FDA approved indications. All of these drugs have been approved for use in rheumatoid arthritis. Most studies compare them to aspirin and there are very few studies comparing them to each other. No study has shown one of the NSAIDs to be more efficacious than aspirin and therefore aspirin remains the drug of choice in the treatment of rheumatoid arthritis and most of the other forms of chronic arthritis. In patients who cannot take aspirin for some reason, these drugs are reasonable alternatives although they are more costly than aspirin. Several of these drugs are approved for use in osteoarthritis and the comparative studies have not shown them to be more efficacious than aspirin. Indomethacin, phenylbutazone, and sulindac have been approved for use in ankylosing spondylitis. Phenylbutazone and sulindac have been approved for use in the acutely painful shoulder although most orthopedists and rheumatologists would treat the acutely painful shoulder with local corticosteroid injections and use aspirin or a nonsteroidal anti-inflammatory drug as an adjunctive form of therapy along with physical therapy. Phenylbutazone, indomethacin, and sulindac are approved for use in acute gouty arthritis. In the hospital setting, particularly in the patient who cannot take anything by mouth, intravenous colchicine is the drug of choice, however.

Naproxen and sulindac are given in twice daily dosage schedules. The half-life of naproxen is approximately 14 hours and of sulindac approximately

TABLE

Nonsteroidal Anti-Inflammatory Drugs

Name	How Supplied	Daily Dose	Indications
Indomethacin (Indocin) MSD	25 mg caps 50 mg caps	75-200 mg	OA, RA, AS, Acute Gouty Arthritis
Phenylbutazone (Butazolidin) Geigy (Azolid) USV	100 mg tab	100-400 mg	OA, RA, AS, Acute Gout, Painful Shoulder, Psoriatic Arthritis
Ibuprofen (Motrin) Upjohn	300 mg tab 400 mg tab 600 mg tab	1200-2400 mg	OA, RA
Naproxen (Naprosyn) Syntex	250 mg tab	500-750 mg	RA
Fenoprofen (Nalfon) DISTA	300 mg pulvule 600 mg pulvule	1200-2400 mg	OA, RA
Tolmetin (Tolectin) McNeil	200 mg tab	600-1800 mg	RA
Sulindac (Clinoril) MSD	150 mg tab 200 mg tab	300-400 mg	OA, RA, AS, Acute Painful Shoulder, Acute Gouty Arthritis

OA — Osteoarthritis
RA — Rheumatoid Arthritis
AS — Ankylosing Spondylitis

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*Assistant Professor of Medicine, Mayo Medical School, Rochester, Minnesota.

18 hours. The other NSAIDs are given three or four times a day.

Caution must be used in giving these drugs to patients who have true aspirin sensitivity with nasal polyps and asthma. All of these drugs, with the exception of phenylbutazone, have demonstrated cross sensitivity with aspirin. In patients truely allergic to aspirin, sodium salicylate would be the drug of choice. All of the nonsteroidal anti-inflammatory drugs can cause upper gastrointestinal tract irritation and ulceration. When compared to aspirin, the incidence of this side effect is less but it still occurs and patients with an ulcer diathesis must be watched carefully when any of these drugs are used. Each of these drugs can interfere with platelet function to decrease adhesiveness and therefore possibly increase bleeding time. Each of these drugs can influence the prothrombin time by interfering with the metabolism of coumadin. They can be used concurrently with coumadin provided their dosage is kept steady. Phenylbutazone is the most hazardous of these drugs because of its hematologic side effects. This drug can be used to treat acute gouty arthritis provided the total dose is limited to five or six days. More chronic administration of this drug runs the unpredictable risk of a cytopenia which may not be reversible.

In conclusion, the proliferation of nonsteroidal anti-inflammatory drugs over the past few years has increased the number of pharmacologic agents available to treat the various forms of arthritis. None, however, has replaced aspirin as the drug of choice in the treatment of the chronic forms of arthritis. Each of the newer drugs is significantly more expensive than aspirin.

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly *Drug Dependence* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused There have been reports of subjects becoming psychologically dependent on diethylpropion The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia. *Use in Pregnancy* Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks *Use in Children*. Tenuate is not recommended for use in children under 12 years of age

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia. One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*. Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema, *Endocrine*: impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia. *Miscellaneous*: A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria

DOSAGE AND ADMINISTRATION: Tenuate (diethylpropion hydrochloride): One 25 mg tablet three times daily, one hour before meals, and in midevening if desired to overcome night hunger. Tenuate Dospan (diethylpropion hydrochloride) controlled-release: One 75 mg tablet daily, swallowed whole, in midmorning Tenuate is not recommended for use in children under 12 years of age.

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References: 1. Citations available on request from Medical Research Department, MERRELL-NATIONAL LABORATORIES, Cincinnati, Ohio 45215. 2. Hoekenga, M T., O'Dillon [Dillon], R.H., and Leyland, H M A comprehensive review of diethylpropion hydrochloride In, Central Mechanisms of Anorectic Drugs, S Garattini and R Samanin, Ed., New York, Raven Press, 1978, pp 391-404

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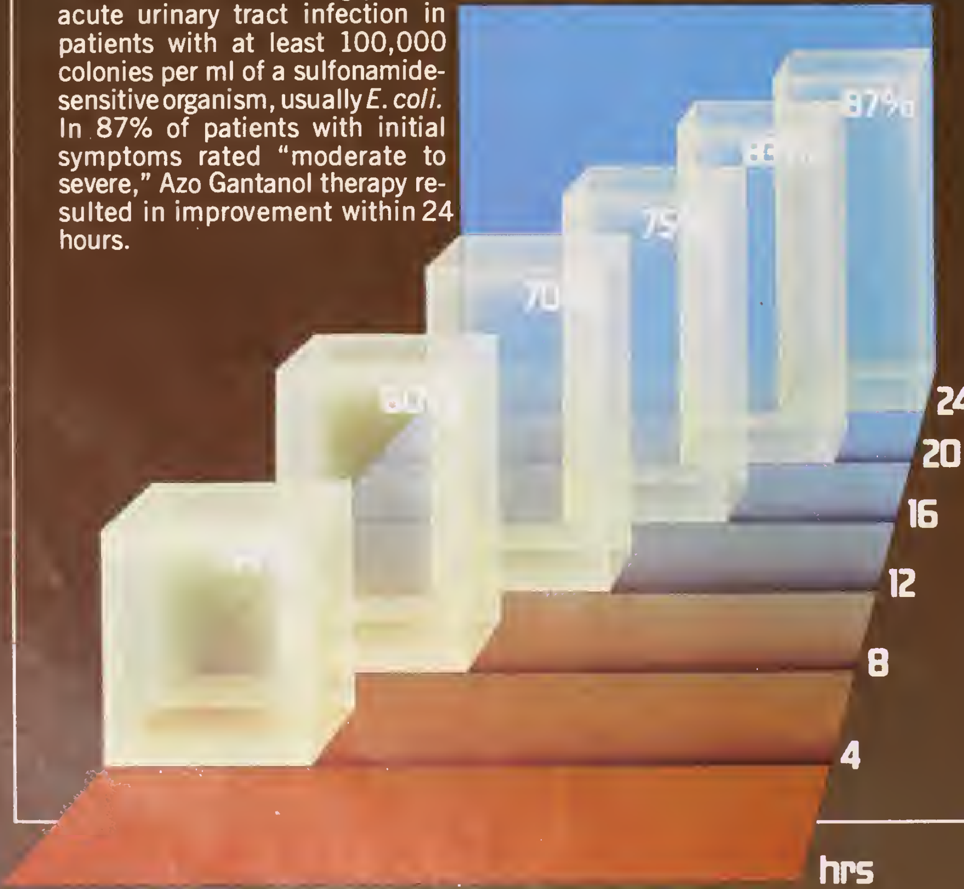

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complicated by pain (primarily pyelonephri
pyelitis and cystitis) due to susceptible org
(usually *E. coli, Klebsiella-Aerobacter, Sta*
coccus aureus, Proteus mirabilis, and, les
quently, *Proteus vulgaris*) in the absence o
obstructive uropathy or foreign bodies. **Not**
fully coordinate *in vitro* **sulfonamide sensi**
tests with bacteriologic and clinical respon
aminobenzoic acid to follow-up culture m
increasing frequency of resistant organism
the usefulness of antibacterials including
fonamides. Measure sulfonamide blood le
variations may occur; 20 mg/100 ml shoul
maximum total level.
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during nursing period; because Azo Ganta
tains phenazopyridine hydrochloride it is
dicated in glomerulonephritis, severe hep
uremia, and pyelonephritis of pregnancy
disturbances.
Warnings: Safety during pregnancy not est
Deaths from hypersensitivity reactions, a
tosis, aplastic anemia and other blood dy
have been reported and early clinical sign
throat, fever, pallor, purpura or jaundice)
dicate serious blood disorders. Frequent
urinalysis with microscopic examination a
ommended during sulfonamide therapy.
Precautions: Use cautiously in patients wi
paired renal or hepatic function, severe a
bronchial asthma; in glucose-6-phosphat
dehydrogenase-deficient individuals in wh
dose-related hemolysis may occur. Mainta
adequate fluid intake to prevent crystallur
stone formation.
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ulocytosis, aplastic anemia, thrombocyto
leukopenia, hemolytic anemia, purpura,
thrombinemia and methemoglobinemia);
reactions (erythema multiforme, skin eru
Stevens-Johnson syndrome, epidermal n
urticaria, serum sickness, pruritus, exfoli
dermatitis, anaphylactoid reactions, perio
edema, conjunctival and scleral injection
sensitization, arthralgia and allergic my
G.I. reactions (nausea, emesis, abdomina
hepatitis, diarrhea, anorexia, pancreatitis
stomatitis); *CNS reactions* (headache, pe
neuritis, mental depression, convulsions,
hallucinations, tinnitus, vertigo and inso
miscellaneous reactions (drug fever, chill
nephrosis with oliguria and anuria, peri
nodosa and L. E. phenomenon). Due to
chemical similarities with some goitrogen
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causes other than infection should be
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treatment with Gantanol (sulfamethoxazo
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Viral Hepatitis in Hospital Personnel in Minnesota

Report of a Statewide Survey

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This study documents for the first time a statewide risk of clinical viral hepatitis infection in hospital personnel (136 cases/100,000 hospital personnel/year.) Age, sex, occupation, work area, date of onset of hepatitis, hepatitis B surface antigen or antibody status, and possible source of infection were determined for Minnesota hospital personnel with viral hepatitis in a two-year period (1974 and 1975). Two hundred cases were documented in personnel during the period. One hundred eighty-nine of the cases may have been occupationally acquired. The ratio of B to non-B hepatitis was 5.1:1. The highest incidence rates occurred in dialysis technicians (10,577 cases/100,000 employees/year) and dialysis nursing staff (10,520/100,000/year). Employees in hospitals with renal dialysis units in the Minneapolis-St. Paul metropolitan area had a mean annual incidence rate of 542/100,000/year compared with 71/100,000/year in metropolitan hospitals without dialysis units. The incidence rates for non-metropolitan hospitals with and without dialysis units were 128/100,000/year and 21/100,000/year respectively.

OCCUPATIONAL VIRAL hepatitis is a significant hazard for medical personnel[1], and its occurrence in employees in various work areas has been well documented[2–10]. The incidence of clinical hepatitis infection in medical and ancillary hospital personnel has been estimated to be three to six times greater than that of workers in other occupations[11]. An investigation of 19 cases of hepatitis in Yale-New Haven Hospital employees over a 13-year period showed an incidence rate of 69 cases/100,000 employees per year as compared with a rate of 15 cases/100,000 population for residents of Connecticut[1]. In another study, over a 4½-year period 79 employees of a university hospital acquired viral hepatitis, 55 cases of which were hepatitis B. Sixty-eight of the personnel worked in either the dialysis unit or clinical laboratory. Incidence rates for employees in these areas over the period were 7.6 per cent and 2.6 per cent respectively[12].

The only published studies on the incidence of hepatitis in hospital personnel have been epidemic investigations or group surveys. The purpose of this study was to determine the incidence of physician-diagnosed clinical viral hepatitis in Minnesota hospital personnel during a two-year period (1974 and 1975), by employee's age, sex, occupation, work area, date of onset, status for hepatitis B surface antigen (HBsAg), and possible source of infection. Incidence rates by geographic location of the hospital and presence or absence of a dialysis unit were also calculated.

Material and Methods

Case Finding

In July 1976, administrators of 182 hospitals in Minnesota were requested by letter to identify all employees diagnosed by a physician as having clinical viral hepatitis in 1974 and 1975. It was suggested to administrators that employee health service, personnel, and infection control committee records be utilized to identify cases. The hospitals included are all those licensed by the Minnesota Department of Health (MDH) (180), a large medical clinic and a regional kidney-dialysis program. The large medical clinic (5,754 employees) and regional kidney-dialysis program (228 employees) were included in the study because 40 per cent and 68 per cent, respectively, of the employees were assigned to hospital locations. All administrators were later contacted by telephone for the information. In addition, all viral hepatitis cases reported to the MDH that occurred in medical and paramedical personnel during 1974 and 1975 were reviewed.

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A case was defined as type B if the employee was positive for HBsAg and was diagnosed by a physician as having viral hepatitis at the time of clinical illness. It is not known which method (agar gel diffusion, complement fixation, or radioimmunoassay) was used to test serum collected at the time of illness for HBsAg. All other cases were considered non-B.

Information about employees' age, sex, occupation, work area, date of onset of hepatitis and HBsAg status was requested from administrators. If information was incomplete, the employee was contacted. One employee had terminated employment with the hospital and could not be located at a forwarding address. Information for that employee was obtained from the attending physician.

Information regarding consumption of raw clams or oysters, use of injected drugs, transfusion of blood or blood products, contact with jaundiced persons or hepatitis patients, percutaneous procedures (surgery, dental work, oral surgery) and known occupational exposures was obtained for each case by interviewing patients (199 cases) or the attending physician (one case).

Personnel Census by Occupation

The number of full- and part-time personnel employed by the 180 hospitals in Minnesota, by occupation, was obtained from the 1975 license applications submitted to MDH. The personnel offices from the medical clinic and regional kidney dialysis program provided similar information. The total number of hospital personnel in the state was obtained by adding the mean number of full- and part-time personnel employed (69,452) during 1974 and 1975.) Information regarding the number of dialysis technicians and nursing personnel employed in each dialysis unit during 1974 and 1975 was obtained from the respective personnel offices.

Occupational definitions used in the study were those included in the MDH guidelines for hospital license application[13]. Although the MDH guidelines define a dialysis technician as "other specialist", we considered them separately in this study. Data on nursing personnel in dialysis units were also analyzed independently.

Outbreak Definition

We attempted to determine the number of nosocomial outbreaks of hepatitis among personnel. We defined an outbreak as two or more cases of hepatitis B in one work area within one month, or two or more cases of non-B hepatitis in one work area within two weeks.

Results

Over the two-year period, 32 institutions (18 per cent) identified cases in their personnel. One hundred-fifty (82 per cent) institutions did not report any hepatitis cases among their personnel. All institutions reviewed employee health service and administration records to identify cases.

Two hundred cases of physician-diagnosed clinical viral hepatitis were identified in hospital personnel in the state of Minnesota for 1974 and 1975. Forty-three were documented by MDH during two separate epidemic investigations at a large metropolitan hospital*[14]. Of the remaining 157 cases, 59 (38 per cent) were reported to MDH by the normal surveillance methods.

Overall, 193 (97 per cent) of the 200 cases were tested for the presence of HBsAg at the time of illness (Table 1). Results of initial HBsAg testing results were compatible with physicians' diagnoses for all but one employee. One employee reported by a physician as having non-B hepatitis was positive for HBsAg. This case was considered type B.

Eleven viral hepatitis cases in employees were due to nonoccupational exposures. Nine cases of non-B hepatitis occurred in two foodborne outbreaks, one case of hepatitis B followed a surgical procedure involving blood transfusions, and one case of hepatitis B developed after sexual contact with a HBsAg-positive individual. These cases are not included in the analysis.

The 189 remaining cases of hepatitis are defined as

TABLE 1

Analysis of Hepatitis B Surface Antigen (HBsAg) Test Results and Physician Diagnosis

Physician Diagnosis	HBsAg Positive	HBsAg Negative	Not Tested	Total
B	159	0	0	159
Non-B	1	33	7	41
Total	160	33	7	200

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*Levy BS, Osterholm MT, Washburn JW, et al: Hepatitis among employees of Hennepin County Medical Center in 1975: a follow-up investigation. Paper prepared for the Minnesota Department of Health, April 2, 1976.

possible occupationally acquired hepatitis. One hundred fifty-eight were hepatitis B and 31 non-B hepatitis. Seventy-one cases of hepatitis B and 22 cases of non-B hepatitis were detected in 1974, while 87 cases of hepatitis B and nine cases of non-B hepatitis were detected in 1975.

Possible occupationally acquired cases of hepatitis B occurred during each of the 24 months studied (Figure). The highest number of cases of hepatitis B (13 cases) occurred in October 1975. Eight were associated with an outbreak on a renal-infectious disease ward in a metropolitan hospital. Non-B hepatitis was identified in personnel in 11 different months. The largest number of non-B hepatitis cases occurred in June 1974. At least four of the cases occurred in personnel caring for patients who became ill as a result of a large hepatitis A foodborne outbreak that occurred in late April and early May 1974 in Minneapolis.

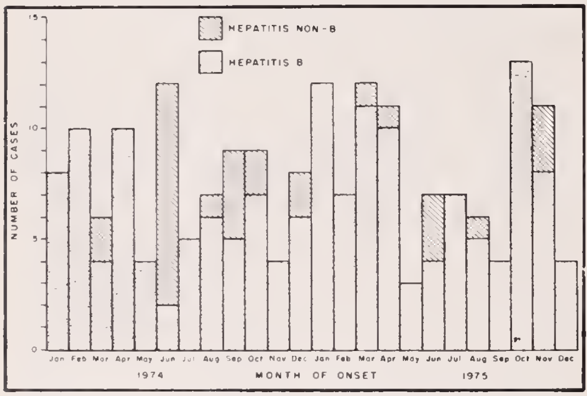

Figure — cases of possible occupationally acquired clinical viral hepatitis in hospital personnel in the state of Minnesota according to month of onset, 1974 and 1975.

The mean annual incidence for possibly occupationally acquired clinical viral hepatitis in hospital personnel during 1974 and 1975 was 136 cases/100,000 personnel. The rate was 132 cases/100,000 personnel in 1974, and 140 for 1975. All incidence rates are reported per 100,000 personnel. During the same time period, the annual mean incidence of viral hepatitis cases in the general population that were reported to MDH was 24.5/100,000[15].

Specific incidence rates in personnel for hepatitis B were 102 for 1974 and 126 for 1975. Incidence rates for non-B hepatitis were 30 and 13, respectively. The ratio of hepatitis B to non-B hepatitis was 5.1:1 during the two-year period. Table 2 shows the distribution of these cases by age, sex and diagnosis.

The highest mean annual incidence rates by occupation were found for dialysis technicians and dialysis nursing personnel (Table 3). High incidence rates during both years also occurred for the clinical laboratory service and the physician service. Physician service includes all physicians, residents, interns, or medical students who are contracted by the hospital for services or who are in a hospital training program. No cases of hepatitis were found in dental service personnel associated with these institutions.

The mean annual average number of employees in Minnesota hospitals and the number of cases by hospital category is given in Table 4. Metropolitan area hospitals (32) are those in the seven county Minneapolis-St. Paul metropolitan area. All other hospitals in the state are defined as non-metropolitan.

The mean annual incidence rate in 1974 and 1975 for personnel who worked in hospitals with renal dialysis units was 397, while the rate for personnel in hospitals without dialysis units was 38 ($p<0.0001$ by 2×2 X^2 test with Yates correction). Metropolitan-area hospital employees had a rate of 269 as compared with 39 for non-metropolitan employees ($p<0.0001$). Metropolitan-area hospitals (32 hospitals) include all those in the seven county Minneapolis-St. Paul metropolitan area. Non-metropolitan hospitals include all other hospitals (150 hospitals) in Minnesota. Employees of metropolitan hospitals with dialysis units had a rate of 542, while employees of non-metropolitan hospitals with dialysis units had a rate of 128 ($p<0.0001$). In metropolitan hospitals without dialysis units, the rate was 71 as compared to 21 in the non-metropolitan hospitals without dialysis units ($p<0.0001$).

TABLE 2

Analysis of Cases by Age, Sex and Diagnosis

Age Group	Male			Female			Total		
	B	Non-B	Total	B	Non-B	Total	B	Non-B	Total
19-29	32	3	35	89	18	107	121	21	142
30-39	6	1	7	16	2	18	22	3	25
40+	5	0	5	10	7	17	15	7	22
Total	43	4	47	115	27	142	158	31	189

TABLE 3

Analysis of Cases by Occupational Category

		Cases		Mean annual
Occupation*	1974	1975	Total	incidence rate/100,000
Dialysis technician	6	5	11	10,577
Nursing service (dialysis units)	19	25	44	10,520
Clinical laboratory service	18	21	39	568
Physician service	9	10	19	247
Radiological service	3	1	4	164
Health education	1	0	1	162
Pharmacy	1	0	1	145
Nursing service (non-dialysis units)	27	27	54	96
All other health professions	2	3	5	83
Therapeutic service	4	0	4	82
Administration	1	1	2	45
All other non-health professions	2	3	5	11
Dental service	0	0	0	0
Medical records service	0	0	0	0
Physician extender	0	0	0	0
Total	93	96	189	136

*Occupational definitions are from the Minnesota Department of Health Guidelines for Hospital License Applications.

TABLE 4

Analysis of Cases by Hospital Category and Work Area

	Hepatitis cases		Mean annual
Hospital category	Non-B	B	number of personnel
Metropolitan*	26	132	29,338
Hospitals with dialysis units	15	119	12,370
Dialysis personnel	3	56	196
Non-dialysis personnel	12	63	12,174
Hospitals without dialysis units	11	13	16,968
Non-metropolitan*	5	26	40,114
Hospitals with dialysis units	0	17	6,629
Dialysis personnel	0	6	57
Non-dialysis personnel	0	11	6,572
Hospitals without dialysis units	5	9	33,485
Total	31	158	69,452

*Metropolitan area includes all hospitals (32) in the seven county Minneapolis-St. Paul metropolitan area. Non-metropolitan area includes all other hospitals (150) in Minnesota.

TABLE 5

Mean Annual Incidence Rate per 100,000 Personnel in Dialysis Technicians and Dialysis Nursing Personnel Compared with Non-Dialysis Personnel in Minnesota

	Location		
Work Area	Metropolitan*	Non-metropolitan*	Total
Dialysis personnel	15,051	5,263	12,846
Non-dialysis personnel	308	84	229
Total	542	128	397

*Metropolitan area includes all hospitals (32) in the seven county Minneapolis-St. Paul metropolitan area. Non-metropolitan area includes all other hospitals (150) in Minnesota.

In hospitals with dialysis units, the mean annual incidence rate for dialysis personnel (dialysis technicians and dialysis nursing personnel) was 12,846 compared with 229 for non-dialysis personnel ($p<0.0001$) (Table 5).

Clinical laboratory employees of hospitals with dialysis units had a mean annual incidence rate of 1051 while the laboratory employees of hospitals without dialysis units had a rate of 214 ($p<0.0001$) (Table 6).

Nineteen nosocomial outbreaks involving 51 employees were identified during the two-year period: 16 outbreaks of hepatitis B involving 44 employees and three outbreaks of non-B hepatitis involving seven employees. Fourteen of the 16 hepatitis B outbreaks involving 40 employees were in personnel of the dialysis unit or renal service. The other two outbreaks involved four medical laboratory personnel.

Discussion

This study documents for the first time a statewide increased risk of clinical viral hepatitis infection in hospital personnel. However, the incidence rates obtained in this study must be qualified.

No effort was made to subtract nonsusceptible personnel (those who had already had hepatitis B or non-B hepatitis) from the number of employees in any work area before calculating the incidence rates. Subtracting nonsusceptibles would result in higher calculated incidence rates for personnel in high-risk occupations or work areas. Nor was any effort made to determine the actual number of hours or weeks that each employee was at risk. Incidence rates were calculated on the mean annual number of employees (both full- and part-time) in the 182 institutions for the two-year period.

A preferable method of calculating incidence rates would be to base them on person-hours or person-weeks of exposure, subtracting for nonsusceptible personnel in the denominator. The data were not available to perform these calculations.

It has recently been suggested[16,17] that it is not necessary to utilize enteric precautions for patients with hepatitis A after they have become icteric. However, we have documented four cases of hepatitis A in personnel which occurred approximately one month after caring for three different hospitalized patients who became ill as a result of a large food-borne outbreak. All the patients considered as probable sources were icteric on hospital admission. The employee cases had no other known contacts. Our results suggest that in some instances a patient hospitalized for icteric type A hepatitis may be communicable and enteric precautions should be utilized.

The mean annual incidence rates in dialysis technicians and dialysis nursing staff are substantially higher than any of the other incidence rates. Clinical laboratory personnel in hospitals with dialysis units had significantly higher incidence rates than laboratory personnel in hospitals without dialysis units, regardless of location. This increased risk could be at least partially explained by contact with blood or other body fluids from dialysis patient cases.

It has previously been reported that dental personnel are at an increased risk of acquiring viral hepatitis[18-20]. However, no cases of hepatitis were reported in the 69 hospital employees in dental service during 1974 and 1975.

This study documented that 38 per cent of the hepatitis cases occurring in hospital personnel had been reported to MDH by the normal surveillance methods. Normal surveillance includes cases of hepatitis reported by physicians, by the Minneapolis War Memorial Blood Bank, by other health personnel, and cases identified by contacts requesting immune globulin from MDH. The percentage reported is greater than the estimated 10-20 per cent reporting for medically diagnosed cases of hepatitis[21]. However, it does document the under reporting of medically diagnosed viral hepatitis in states where such reporting is required by regulation. It also suggests there would be less difference between the incidence rates for the hospital personnel obtained in this study and those previously documented for the general population with normal surveillance if equally vigorous surveillance programs were carried out.

Overall, 97 per cent (193 cases) of employees diagnosed with viral hepatitis were tested for the presence of HBsAg at the time of illness. In Minnesota from June 1974 to June 1975, 53 per cent of all cases reported to MDH were tested for HBsAg[15]. Nationally, 46 per cent of all cases of viral hepatitis reported to the Center for Disease Control (CDC) from January 1, 1975 to December 31, 1975 were tested for HBsAg[22]. Physician diagnoses agreed with initial HBsAg results in all but one (0.5 per cent) of the 200 cases. In all reported cases in Minnesota from June 1974 to June 1975, 9 per cent of physician diagnoses of hepatitis A or B were not compatible with HBsAg testing results[15].

Although 142 (75 per cent) of all possibly occupationally acquired hepatitis cases occurred in personnel 19-29 years of age, we have not determined if there is an increased relative risk of infection. Other explanations for the increased number of cases may be that a greater number of personnel were employed in this age group, or personnel in older age groups may have had hepatitis previously and were no longer susceptible. The data with which to make these calculations were not available.

Employees of metropolitan area hospitals had a significantly higher incidence rate of hepatitis than non-metropolitan area employees. This difference was also evident when hospitals without dialysis units in the metropolitan and non-metropolitan areas were compared. Previous studies showed that 75 per cent of all hepatitis cases reported in Minnesota occurred in those who lived in the seven-county Minneapolis-St. Paul metropolitan area[15]. The higher number of hepatitis cases in the metropolitan area population could explain the higher incidence of hepatitis in metropolitan hospital personnel. Also, the non-metropolitan hospitals may differ in many respects from the metropolitan. The latter are more likely to have a younger staff because of training facilities for medical students, interns, residents, student nurses, etc. Small hospitals in rural areas may be more likely to have part-time help than those in major centers, falsely increasing the denominator compared with person-days of risk. Age, socio-economic status, and ratio of full to part-time help may have had an influence on the rates. However, the data was not available to examine this.

Hepatitis cases were not randomly distributed throughout all of the hospitals in the state. Four of five (80 per cent) institutions with dialysis units in the metropolitan area were responsible for 123 (64 per cent) of the 189 cases. The four institutions routinely dialyze HBsAg-positive patients. The fifth institution had only five cases (three per cent) of hepatitis, all of which were non-dialysis associated. This institution refused to dialyze known HBsAg-positive patients. All non-metropolitan dialysis hospitals routinely dialyzed HBsAg-positive patients.

The ratio of hepatitis B to non-B hepatitis (5.1:1) was higher for medical personnel than for the general population. For the same two-year period the ratio of hepatitis B to non-B hepatitis cases reported for the general population in Minnesota was 1:1.2. This is not unexpected, considering the modes of transmission for viral hepatitis.

Summary

This study documents the high risk of acquiring clinical viral hepatitis for hospital personnel on a statewide basis in Minnesota. Most of the risk in this group is due to the occurrence of hepatitis B infection in personnel who work in renal dialysis or a hospital laboratory. Incidence rates also appear to be related to the geographic (metropolitan or non-metropolitan) location of the hospital. We are confident that these results are not unique to Minnesota, and we encourage other state health departments to conduct similar studies. Such information will be useful in defining the actual risk of viral hepatitis for hospital personnel according to occupational category and work area. These data may also be of importance in identifying personnel who can benefit from hepatitis B vaccine when it becomes available.

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Classified Advertising 691
First Bank Minneapolis 646
Hearing Instrument Dispensers Guild 652
Lilly, Eli & Co. 670
Marquette National Bank .... Cover 2
Mead Johnson Pharmaceutical Division 642
Medical Protective Company 676
Merrell-National, Inc. 640, 641, 664, 665, 666, 680, 681
Merck Sharp Dohme 640
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(Continued to page 692)

(Continued from page 691)

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WANTED— M.D. or D.O./FAMILY PRACTICE to join gr. of 3 FP/MD's. Exc. new clinic attached to 120 bed hosp. Full hosp. priv. avail. Salary 1st yr. then may join corp. Thriving comm. of 10,000 + with lg. drawing area. Fine recreational and social area with first class school system & all churches avail. Easy freeway access to metro area. Contact Family Clinic, 808 3rd St. S.E., Little Falls, MN 56345 or call collect D. R. Seifert M.D. (days) 1-612-632-2301, (evenings) 1-612-632-9150.

ORTHOPAEDIC SURGEON, Internist and OB-GYN for multi-specialty group with a Family Practice Department, Crookston, Minnesota. New clinic facility, full partner in one year. Located in the heart of the Red River Valley with stable economy. Call R. R. Schnabel, M.D. collect at 218-281-3184, Crookston, Minnesota.

OBSTETRICIAN-GYNECOLOGIST, to join 11 member primary care group. 7 Family Physicians, 2 Internists and 2 General Surgeons. Large patient population, newly remodeled and expanded Clinic facility approximately 6 blocks from modern, well equipped 99 bed hospital. Rural community 45 minutes South of the Metro area on 35W. Salary guarantee first year. For more information please contact: Darral Mischke, Clinic Administrator, Faribault Clinic, Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

PSYCHIATRIST — Board Eligible or Certified to take charge of a 30-bed ward in this 409 bed, University affiliated VA Medical Center located in the Black Hills. Position offers clinical, and possible academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. Area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD. 57741. Phone (605) 347-2511, Ext. 497. Equal Opportunity Employer.

FAMILY PRACTITIONER, OB-GYN, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

FAMILY PHYSICIAN SEEKING POSITION Young, Residency trained, Board Certified Family Practitioner, with practice experience in Minnesota, desires part time position in or near Minneapolis-Saint Paul area. Practice and/or administrative opportunities considered. Write: Minnesota Medicine — 545, Suite 900 101 E. 5th St., St. Paul 55101.

INTERNIST: Certified or Board Eligible to join the staff of this 409 bed, University affiliated VA Medical Center located in the Black Hills of South Dakota. Position offers both clinical and academic duties in this modern facility. Excellent salary and benefits, including malpractice coverage. This area has an abundance of recreational activities, and no state income tax. Perfect area for children. Modern living quarters are available on hospital grounds at reasonable rental rates. Public Law 95-201 requires proficiency in spoken and written English. Write or phone: Dr. Charles E. Townsend, Chief of Staff, VA Medical Center, Fort Meade, SD 57741. Phone 347-2511, Ext. 497. Equal Opportunity Employer.

OUTSTANDING OPPORTUNITY for two family physicians and one surgeon to join young group of six, Board certified family physicians, one general surgeon who is a fellow of the American College of Surgery, one physician's assistant and one Ph.D. family counselor. The new 11,000 square foot clinic is located just Southwest of the Minneapolis metropolitan area and offers excellent access to the downtown area while offering the advantages of small-town living. The Shakopee area also possesses an outstanding school system. In the Summer of 1980, it is anticipated that an 8,000 square foot expansion will be completed by the clinic and will be located in Prior Lake, Minnesota. Both the clinics will be serviced by St. Francis Hospital (126 bed, full-service facility). The Shakopee Medical Center offers early buy-in possibilities and excellent fringe benefits. For further information contact Donald Lynch, M.D. or David C. Fleming, Clinic Administrator at the Shakopee Medical Center, 1335 East Tenth Avenue, Shakopee, MN, 55379 or phone 612-445-1305.

WANTED: GP to join two GP's in practice in rural community northern Minn. Mod. clinic bldg. with good xray & lab facilities. 40 bed hosp; 100 bed nursing home. Also need locum tenans for summer vacations. Contact W. A. Pinsonneault, MD, Warren Clinic, box 107, Warren, MN 56762 (218) 745-4151.

APPLICATIONS WELCOMED from board-qualified or certified radiologists. Large teaching hospital, upper midwest; University affiliation. Subspecialty training in nuclear medicine desirable. Box 529, Minnesota Medicine, 101 E. 5th St., St. Paul 55101.

FAMILY PHYSICIAN to join expanding group of family physicians. Downtown Minneapolis location adjacent to Metropolitan Medical Center. Contact Donald Blowers, M.D., or Roxanne Butler, Business Manager, Parkside Family Physicians, P.A., 825 South 8th St., Mpls., Mn. 55404. Phone 375-1700.

PSYCHIATRIST. University of Minnesota, Minneapolis-St. Paul. Board certified or board eligible psychiatrist to work in the Boynton (student) Health Service outpatient mental health clinic. Practice modalities include individual, couple, group psychotherapy, and crisis intervention. Nine month appointment, coinciding with academic year plus option to work one five-week summer term. Position available January 2, 1980, Generous fringe benefits. Salary negotiable and commensurate with training and experience. University of Minnesota is an Affirmative Action/Equal Opportunity Employer. Send resume and three letters of reference by November 1, 1979 to: Paul Rupprecht, Ph.D., Director, Boynton Health Service. 410 Church St. S.E., University of Minnesota, Minneapolis, Minnesota 55455 (telephone (612) 373-4022).

INTERNIST Four Board Certified Internists have need for associate to join a 14 man multispecialty group with modern fully equipped facility across street from 200 bed general hospital and rehabilitation center. Hospital has recently completed 6 million dollar remodeling and modernization project. Medical catchment area of 100,000. Located in a small, friendly city of 13,000 with excellent schools, recreational areas. Interested applicants should call or write: Robert A. Nelimark, M.D. or Harlan A. Hillmer, Administrator Lenont-Peterson Clinic, Ltd., 820 North Ninth Street, Virginia, Minnesota 55792. Phone: (218) 741-4292.

MEDICAL OFFICE EQUIPMENT and furniture: examining tables, mercury manometers, office desks, dictaphone, EKG, diathermy, ultra-sound, electric typewriter, 100 MA picker X-Ray, copying machine, file cabinets and other misc. Phone V.A. Doms, M.D., Elbow Lake, Minn. 218-685-4886 or write box 4041.

(Continued on page 694)

(Continued from page 693)

WANTED — Family practitioner preferably board eligible or certified — at once. Liberal vacations, etc. Salary to be negotiated. Early partnership. Write the Osseo Clinic, P.A., Osseo, Minn. 55369 or call collect 1-612-425-2117.

WANTED: Family Practice physician to join group of four. Clinic situation ½ mile from modern 280 bed hospital. Extensive privileges available to qualified Family Practitioner. Clinic handles a wide variety of patient problems including surgery and obstetrics. Excellent area for potential growth for medical practice. For more information, contact John C. Bordwell, M.D., or East Main Clinic, 850 E. Main Street, Anoka, MN 55303, phone (612) 421-7070.

ENDOSCOPIST/GASTROENTEROLOGIST or internist with sub specialty in gastroenterology and endoscopy, to join young family practice group of 9 family physicians and a general surgeon. Contact: Peter A. Setness, M.D. Doctors' Clinic, LTD. 121 S.E. 11th Ave. Forest Lake, MN (612) 464-7100.

OPENING FOR Family Practice Physician to join group of three with multi-specialty services available in new building — St. Paul and Northern Suburbs. Experienced preferred. 487-2831.

WANTED Family physician, board certified, for full-time faculty position at Hennepin County Medical Center. Inquiries to: Eldon Berglund, M.D., Department of Family Practice, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55415. (612) 347-3103.

75 MINUTES from Minneapolis. Group of four Family Physicians wants to add a surgeon and another Family Physician. Beautiful city with lakes + parks. Incorporated group which stresses family life and free time. Minnesota Medicine, (548) 101 E. 5th St., #900, St. Paul, 55101.

INTERNIST wanted by 9 person medical group in Alexandria, Minnesota. Please contact Steve Henry, M.D., 610 Fillmore, Alexandria, MN. 56308. Telephone (AC 612) 763-5123.

EXCELLENT OPPORTUNITY for two or three family practitioners in small, stable economic community serving 15,000 population. Move into a new clinic attached to 38 bed, well equipped JCAH accredited hospital. One physician now working in the four man clinic. No investment is necessary and you'll be guaranteed a liberal salary with many fringes. Enjoy the many advantages of small community living while living in an area that offers diversified recreational activities, excellent schools and a warm environment. Write or call Omer Eischens, Hospital Administrator, Tracy Municipal Hospital, Tracy, Mn. 56175. Phone collect: 507-629-3200.

GENERAL OR FAMILY practice physician — Social Security Disability Determination Services in St. Paul seeking services of a physician on a half-time basis for in-agency consultative services. Responsibilities include end-of-line chart review for medical accuracy and consultant to the quality assurance unit. Employment can be on a contract basis. Contact Irene Pierson, Assistant Director for Medical Services, 460 Metro Square, St. Paul 55101 or (612) 296-4419.

EMERGENCY ROOM MEDICAL DIRECTOR — For large, metropolitan teaching hospital in Minnesota with new Emergency department. Prefer physician with strong emergency background and/or Board Certification in Internal Medicine or Family Practice. Salary is in $40,000 to $60,000 range. Opportunities also available for smaller community — based practice in various specialties. Fees paid by our employer clients. Please direct inquiries to: MEDICAL CAREERS, 825 Nicollet Mall, Suite 633, Minneapolis MN 55402 (612/339-6640) — Perry C. Harrison, Physician Recruiter.

ANESTHESIOLOGIST needed in outstate Minnesota. Should be board certified or eligible. Department has 300+ cases per month. Malpractice insurance paid. $60,000 first year, then buy in. Write: Minnesota Medicine — 547, Suite 900, 101 E. 5th St., St. Paul 55101.

OPENINGS FOR family physicians, internists and psychiatrists in Minnesota's 9 state hospitals. Salary $40,000-$60,000. Regular hours, liberal benefits. Call Ronald C. Young, M.D., Dept. of Public Welfare (612/296-3058).

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Bactrim™ DS Double Strength Tablets

Each tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole.

Just one tablet b.i.d. for 10 to 14 days

- Action at urinary/vaginal/lower bowel sites helps eliminate reservoirs of infecting organisms
- Distinctive antibacterial action plus wide spectrum helps eradicate recurrent UTI
- Low incidence of bacterial resistance in community practice
- Convenient *b.i.d.* dosage provides day-and-night antibacterial control
- Contraindicated during pregnancy and the nursing period. During therapy, maintain adequate fluid intake; perform CBC's and urinalyses with microscopic examination.

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* **It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.** *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis. To date, this drug has been tested only in patients 9 months to 16 years of age who were immunosuppressed by cancer therapy.

The recommended quantitative disc susceptibility method (*Federal Register, 37*:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy. If infection is confined to the urine, "Intermediate susceptibility" also indicates a likely response. "Resistant" indicates that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers; infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform requent urinalyses, with careful microscopic examination, and enal function tests, particularly where there is impaired renal unction.

Adverse Reactions: All major reactions to sulfonamides and rimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblas-ic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, ypoprothrombinemia and methemoglobinemia. *Allergic reac-ons:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum ickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, eriorbital edema, conjunctival and scleral injection, photosensiti-ation, arthralgia and allergic myocarditis. *Gastrointestinal reac-ons:* Glossitis, stomatitis, nausea, emesis, abdominal pains, epatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L. E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

Urinary Tract Infections: Usual adult dosage—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days.

Recommended dosage for children—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. A guide follows:

Children two months of age or older:

Weight		Dose—every 12 hours	
lbs	kgs	Teaspoonfuls	Tablets
20	9	1 teasp. (5 ml)	½ tablet
40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	½ the usual regimen
Below 15	Use not recommended

Pneumocystis carinii pneumonitis: Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100; Tel-E-Dose® packages of 100. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10. *Oral suspension,* containing in each teaspoonful (5 ml) the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole, fruit-licorice flavored—bottles of 16 oz (1 pint).

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Please see back cover.

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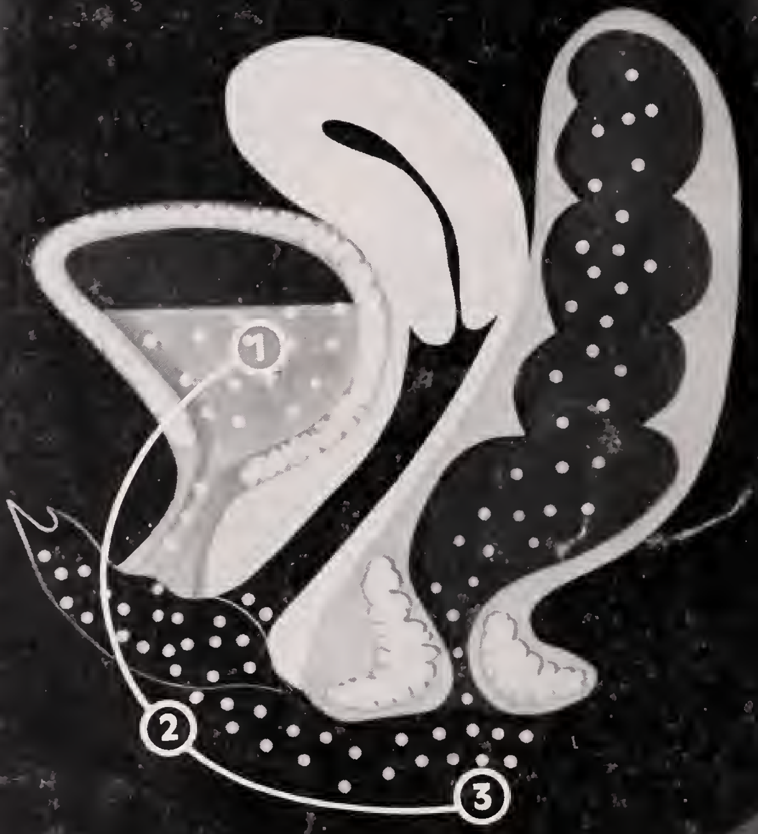

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Bactrim fights uropathogens in the urinary tract/vaginal tract/lower intestinal trac

Please see reverse side for summary of product information.

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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VER PAINTING — "Autumn Tranquility"
Claus A. Pierach, M.D. ... 705

ESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association ... 701

ITOR'S Notebook — **Hospital Solvency and Hospital Marketing**
Richard L. Reece, M.D., Editor-in-Chief ... 703

IGINAL CONTRIBUTIONS

Free Flap Reconstruction of the Lower Extremity
Bruce L. Cunningham, M.D. et al. ... 707
Arthroscopy of the Knee — Another Diagnostic Technique
James D. Priest, M.D. ... 710
Variant A-V Block Secondary to Concealed Conduction
Kyuhyun Wang, M.D. and David A. Berman, M.D. ... 713
Ergot Induced Unilateral Brachial Arterial Occlusion
David DeMartini, M.D. et al. ... 719
Left Atrial Myxoma Presenting as Shock — Diagnosis by Echocardiography
Richard W. Asinger, M.D. et al. ... 723
Limbitrol — A Medical Dream or Nightmare
Theodore G. Larson, M.D. ... 725

IEW — **Shock Lung: An Overview**
Michael A. Harris, M.D. ... 727

TETRICS — GYNECOLOGY

Intrapartum Fetal Heart Rate Monitoring
Emanuel P. Gaziano, M.D. and Donald W. Freeman, M.D. ... 737

UMATOLOGY CORNER —

xtra Articular Manifestations of Rheumatoid Arthritis
H.S. Luthra, M.D. ... 743

IAL ARTICLE — **Prevalence of Intestinal Parasites in a Laotian nmigrant Community**
Neal R. Holtan, M.D. et al. ... 749

ESOTA DEPARTMENT OF HEALTH — **Suggestions for Medical Screening of outheast Asian Refugees**
Andrew G. Dean, M.D. ... 753

ESOTA MEDICAL ASSOCIATION — **Cataract Surgery**
Committee of Ophthalmology ... 759

REVIEWS ... 698

NUING MEDICAL EDUCATION ... 709, 712, 721, 742

IFIED ADVERTISING ... 761

E TO ADVERTISERS ... 730

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Book Reviews

THE NEW WAY TO LIVE WITH DIABETES by Brian Boylan & Charles Weller, M.D. Price: $2.50. Publisher: Doubleday & Company, Garden City, New York.

The 1976 edition is a revised version of a book initially published in 1966. An earnest attempt to present basic information to diabetics and others interested in the disease in a simple easily understood form has been only partially successful.

The classification system used differs from any in common use and separates the diabetic syndrome into components arbitrarily rather than by known pathophysiologic differences. The pathophysiology of the various types of diabetes is hazily described and only partially correct.

Discussion of the role of heredity in diabetes is outdated and in disagreement with current knowledge. A simple autosomal recessive mode of inheritance is presented as factual although this is definitely disproven. According to Rimoin & Rotter in the New England Journal of Medicine, Vol. 295, No. 23, December 2, 1976, "Having to disprove the simple autosomal recessive hypothesis for diabetes mellitus is somewhat like having to disprove the concept that the world is flat." Throughout the book the technique of half-truths and analogies which are not entirely correct are utilized and leave many concepts open to misinterpretations. This is particularly true in the explanation of ketonuria. Also, topics such as hypoglycemic reactions are discussed tangentially without any real definition anywhere in the book.

The recommended use of insulin is conventional and while it disagrees with my personal bias, would find support and approval from many diabetologists. Insulin is discussed only in concentrations of U-40 and U-80 which have largely been replaced by U-100. Recommendations for rotation sites of insulin injections are less than optimal.

The authors have elected to support one side of the controversy involving oral hypoglycemic agents and essentially advise against their use. While many diabetologists support this advice, perhaps the majority feel that oral hypoglycemic agents are of benefit when properly used.

No attempt is made to explain the pathogenesis of chronic complications of diabetes mellitus although the complications themselves are described in limited detail.

Overall this book contains more questionable and outdated information than it does current and correct information. I would hesitate to recommend its use for education of the patient with diabetes mellitus.

G. E. Cotton, M.D.
UMD School of Medicine
Duluth, Minnesota

HELP YOUR DOCTOR HELP YOU—Walter C. Alvarez. Publisher: Celestial Arts, 231 Adrian Road, Millbrae, CA 94030. 1976 Paperback. 126 pages. $4.95.

Twenty-five years ago, I read Dr. Alvarez's book, *Nervousness, Indigestion and Pain.* A few years later, I purchased his book on *Practical Leads to Puzzling Diagnosis.* Although both books were largely anecdotal, I found that his common sense approach was a valuable help in understanding the day-to-day problems of my own patients.

Because I have admired Dr. Alvarez for so many years, I was disappointed in this latest book, *Help Your Doctor Help You.*

The first section of the book is entitled, "Why I Have Written This Book," and is a rambling account of his interest in diagnostic problems and how he began writing for newspapers. He then digresses to describe the availability of medical information tapes but he does not say why he had written the book.

Subsequent chapters seemed just as poorly organized and often directed toward physicians as well as patients.

There are some minor errors. In these days of first year residencies, it seems strange to hear someone speak of interns. At one point in the book, Dr. Alvarez says that a doctor 'spent nine years learning that" when today's medical training is closer to twelve years. He also refers to "specialist or general practitioner," apparently refusing to recognize that family practice is firmly established as a primary care specialty.

There is no index and the short bibliography is not cross-referenced to the text.

Finally, this 125-page paperback is poorly bound, it is printed on coarse paper and there are typographical errors; for example, *thoractic surgeon.* Even in these days of galloping inflation it is not worth $4.95.

John B. O'Leary, M.D.
Minneapolis, Minnesota

CORRELATIVE NEUROANATOMY AND FUNCTIONAL NEUROLOGY by J. G. Chusid. Lange Medical Publications. 448 pages. $10.00.

The fact that Chusid's monograph, Correlative Neuroanatomy and Functional Neurology, is now in its sixteenth edition and has been translated into no fewer than five foreign languages speaks eloquently for its value to students and practitioners of the neurologic sciences. This soft-bound volume presents a wealth of complex material in generally useful concentrated outlines which are both clear and comprehensive. It covers anatomy, physiology, pathology and the principles of neurodiagnosis, and the frequent revisions have kept it almost entirely up-to-date.

The author states that the volume is intended to serve as an aid or supplement to standard neurologic texts. Not only does it fulfill this role, but stands on its own as a valued and current reference work.

This edition contains new material covering advances in neuroendocrinology the use of computerized tomography in neurologic diagnosis, and a number of alterations in the concepts of inflammatory disease affecting the nervous system. Some minor criticisms include the persistence of some outmoded concepts from earlier editions such as the use of subarachnoid saline injections, the inclusion of an excellent table covering neurotransmitters in a chapter on trophic changes, and the failure to cover some advances in neuroradiology such as catheter techniques, magnification and subtraction.

There is no doubt that this book will continue to be one of the most useful aids to study of the nervous system, and its position as a neurological "best-seller" is assured.

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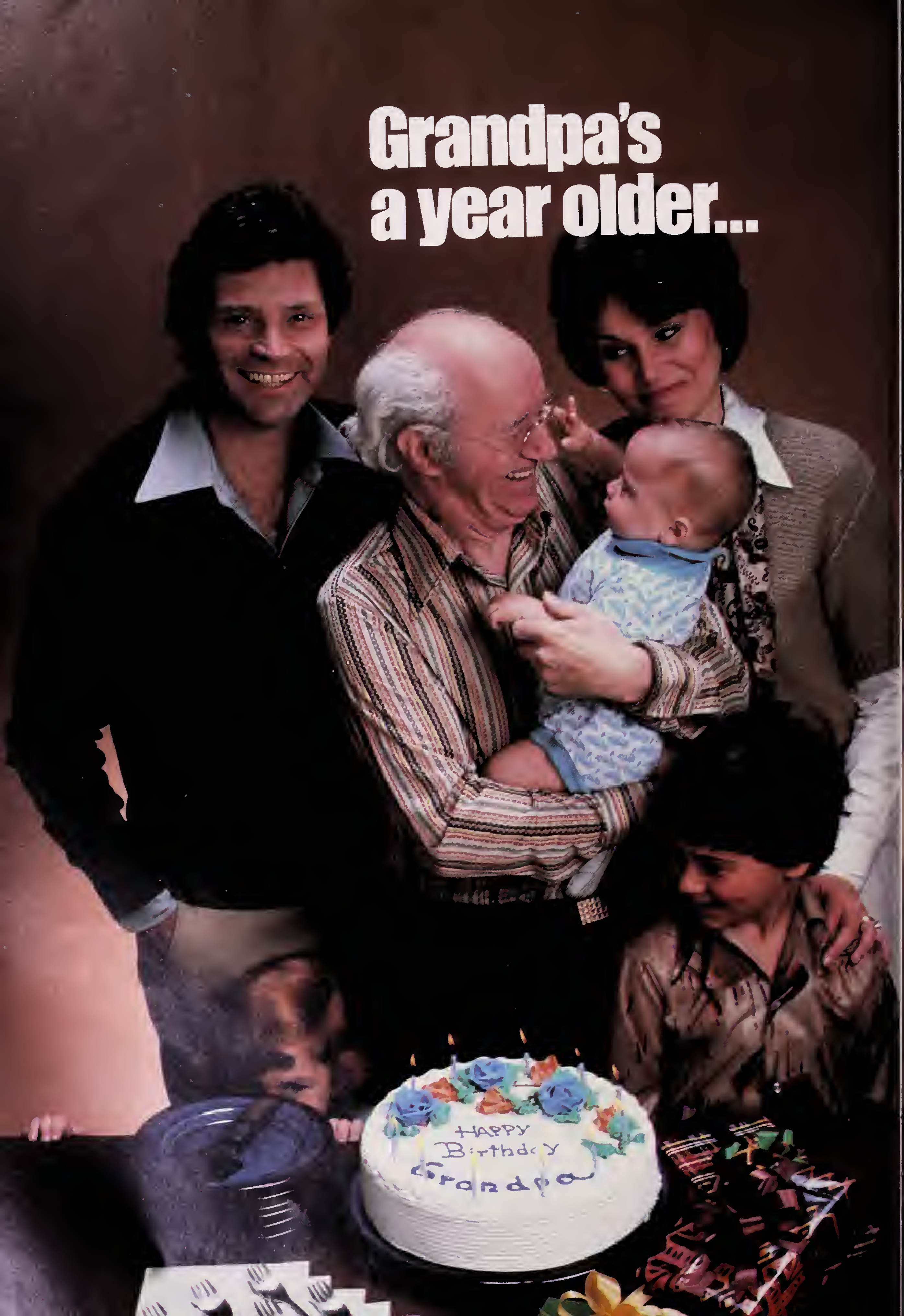
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Caution and appropriate care should be exercised in administering PNEUMOVAX to individuals with severely compromised cardiac and/or pulmonary function in whom a systemic reaction would pose a significant risk and also to patients who have had episodes of pneumococcal pneumonia or other pneumococcal infection in the preceding three years and may have high levels of preexisting pneumococcal antibodies which may result in increased reactions, mostly local but occasionally systemic. Available data suggest that revaccination before three years may result in more frequent and severe local reactions at the site of injection, especially in persons who have retained high antibody levels.

Children under two years of age may not obtain a satisfactory antibody response to some pneumococcal capsular types. Therefore, the vaccine should not be used in this age group.

ADVERSE REACTIONS: Local erythema and soreness at the injection site, usually of less than 48 hours' duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX (containing 14 capsular types) in 26 adults, 24 (92%) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination. Low-grade fever (less than 100.9°F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102°F has been reported.

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NOTE: Administer subcutaneously or intramuscularly. *DO NOT GIVE INTRAVENOUSLY. DO NOT GIVE INTRADERMALLY.*

STORAGE AND USE: Store single-dose prefilled syringes and unopened and opened vials at 2-8°C (35.6-46.4°F). The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% added as preservative.

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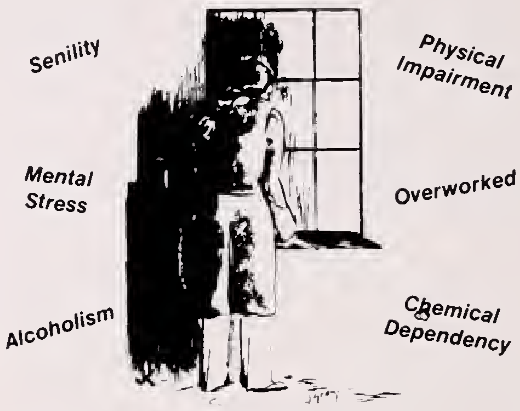

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President's Letter

The value of teamwork in achieving a desired result is never more obvious than during the fall season. Then baseball teams are racing for the pennant. Football is everywhere, and the symphony orchestra is under way for another season. Teamwork is an essential for success in any of these activities.

Health care planning also requires teamwork. A vitally important component of that team is the representative of organized medicine. As our advocate, that person stands for quality medical care and is knowledgeable about cost. His/her position should result from a distillate of the combined wisdom of the membership. The strength of his/her voice is proportional to the size of his/her constituency. For these reasons (wisdom and strength) we need every medical student, resident and licensed physician as team members of the federation of medicine.

I am concerned that the Interspecialty Council of the Minnesota Medical Association formed some three years ago has still not organized itself into an effective team. Some specialty societies have exhibited a certain disdain for the affairs of organized medicine and wish to concern themselves solely with matters of scientific interest. I believe that this is no longer a realistic attitude. Other societies have promoted their special interests without enlisting the full support of the medical association. This is short-sighted and wasteful in that it does not take advantage of available counsel and the strength of the organization. In the matter of legislation, this often fragments and weakens our overall effort and is frequently somewhat confusing to the legislator.

I would hope that the officers of the individual societies would take immediate action to organize themselves more effectively in the Interspecialty Council. To this end the MMA would be willing to make staff help available to each of the societies on a time-cost basis. Such an arrangement would preserve individuality of the specialty society and yet allow for easier coordination into the whole. Improved efficiency and economy of administration should result. The MMA wants to be able to call upon the expertise of individual societies on an Ad Hoc basis, and such staff coordination would be most helpful.

I would propose that once strengthened and properly organized, the Interspecialty Council should request representation in the House of Delegates. This would allow matters of special interest to be scrutinized, criticized, refined, and strengthened in the forum of the Council before appearing on the floor of the House. It goes without saying that if such representation was granted, it would be a requisite that members of the specialty society should also be members of the MMA.

The objective is to strengthen the MMA team. The purpose is to win better medical care for society.

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

Pause for a moment and try to imagine your community without the many services offered by the United Fund Agencies — then, in your own self interest, give generously. F.E.J.

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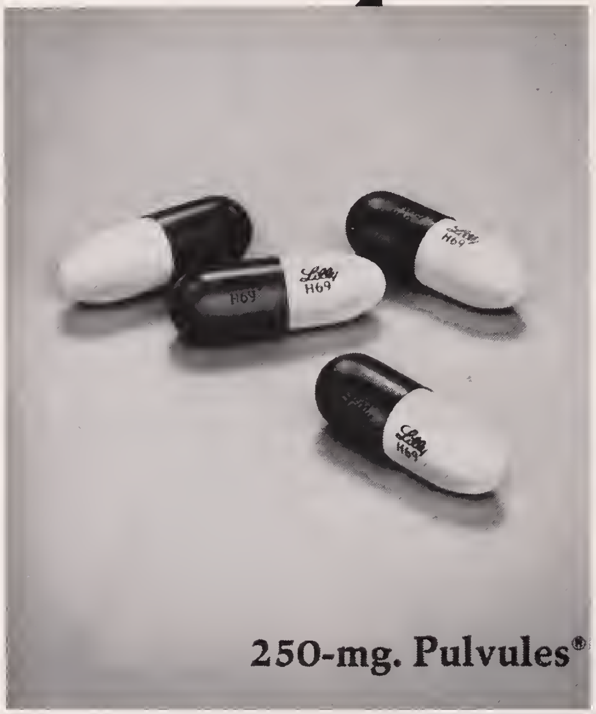
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Editor's Notebook

Hospital Solvency and Hospital Marketing

"Under tremendous competitive pressure to attract patients, hospitals are turning to a host of promotional techniques, ranging from low-key, "image" advertising to high-pressure hustling."

Joann Lublin, "Hospitals Turning to Bold Marketing to Lure Patients and Stay in Business" *Wall Street Journal*, September 11, 1979

Three years ago, in an editorial "Financial Squeeze on Hospitals: Implications for Practicing Physicians,"[1] I said many hospitals were in precarious financial shape, and many would resort to marketing to survive. Among the marketing strategies hospitals would use, I predicted these:

"1. In a broad sense, hospitals will portray the image of community health centers.
2. This image will broaden their base of support, and give them the opportunity to set up health fairs, preventive health clinics, and special clinics to serve patients in their immediate communities.
3. Hospitals will establish special programs to serve those patients who are 'in need' of their services, e.g. the elderly patients with special diseases, e.g. malignancy or neurological disorders.
4. Hospitals will establish 'outreach clinics,' staffed by paid hospital physicians, for drugs, alcoholism, smokers, special diseases, and dieting disorders, to bring more patients under their sphere of influence.
5. Hospitals will organize HMOs so they can capture large organizational audiences, assuring themselves of a stable patient base.
6. Hospitals will become more consumer-oriented, trying to achieve more humane internal design, more warmth on the part of nurses, a better quality of food, and more private rooms with the amenities.
7. Hospitals will launch capital fund drives with prominent businessmen and physicians as prime targets.
8. Hospitals will establish multiple publications with targeted mailing lists, to community leaders, to employees, to potential donors, to physicians, and to patients, in order to inform those in the outside world of their services and to solicit their support.
9. Hospitals will increasingly hire more MDs to staff the institution at all hours, to cover the emergency rooms, to keep the various clinics running, and to run 'outreach clinics' at sites removed from the hospital.
10. Hospitals will employ professional fund raisers, directors of development, and directors of community affairs, to contact affluent donors, to raise funds from government granting agencies and philanthropic organizations, and to keep the community 'informed.' "

Well, what has happened since the 1976 editorial?

Hospital Solvency

This year Philip Kotler, Professor of Marketing at Northwestern University and author of *Marketing for Nonprofit Organizations*, predicted: ". . . between 1,000 and 1,500 hospitals (of the 7,000 in the U.S.) will close in the next five years."[2,3] He thinks those that will survive will have marketing programs, and those that will fold will do so because they "do nothing but pray".[3]

If Kotler's figures are accurate, 15 to 20 percent of U.S. hospitals will be shut down by 1985. Why the high attrition rate?

1. Public outcries to brake health care costs inflation by closing beds and restricting expansion.
2. Proposition-13 inspired tax revolts which are forcing public hospitals, e.g., in New York City and other large cities, to shut their doors.
3. Health Service Agencie's (HSAs) policies, which call for bed reductions and which consolidate specialized resources in larger hospitals at the sacrifice of smaller institutions.
4. 1976 HMO Amendments (PL-460) which have made it easier to launch new HMOs and expand existing ones. (The central purpose of HMOs, after all, is to reduce hospital use.)
5. New technologies — brain and body scanners, facilities for such procedures as hip replacement and coronary bypass, and laboratory computer systems — which require large capital outlays and intricate financing.
6. Government imposed cost-containment measures, viz. Medicare and Medicaid reimbursements at, or below, the direct cost of services.
7. Government regulations, the satisfying of which consumes roughly 25 percent of the total hospital budget (or $40 a day for each patient).[4]
8. An economic recession which is inducing patients to postpone elective procedures or to seek outpatient care.

Hospital Survival

Given the above pressures, how do hospital administrators help their institutions survive? After all, administrators are hired for that purpose. As I noted in my earlier editorial, administrators have these things they can change: (1) price and reimbursement formulas; (2) patient volume mix; (3) material and nonlabor purchases; (4) hiring; (5) wage and salary levels; (6) capital investments; (7) financing; and (8) marketing. Of these options, marketing is currently the one most discussed, though all variables must be tinkered with to assure survival. Perhaps because marketing is a positive approach for at least one who is "doing something," hospital marketing is the hottest thing going in hospital administrative journals.[5-10]

And yet, when physicians discuss hospital marketing, they usually do so negatively, citing blatant advertising or instances such as these:

- Sunrise Hospital in Las Vegas faced low occupancy rates on weekends, so the hospital offered a 5¼ percent weekend discount and a chance on a $4000 cruise anywhere.
- Orlando Regional Medical Center in Orlando, Florida, recently launched a $40,000 physical fitness program, featuring an outdoor track, lockers, and an exercise room.
- Westlake Community Hospital in Melrose Park, Illinois, paid for a physician's ski trip expenses and his condominium rent because he was a potential "heavy admitter".
- Orange County California hospitals recruit doctors by offering leased luxury cars, paid vacations in the Bahamas, and bonuses for maintaining high admissions.

These marketing activities are exceptions, but they highlight the trend of hospitals towards marketing. According to a 1979 survey of 191 hospital administrators, these are marketing practices now being employed in their hospitals.

- Attitude surveys of current and discharged patients (70 percent).
- Studies of services offered by other hospitals (64 percent).
- Formal definitions of hospitals' "target market" (59 percent).
- Development of a demographic profile of patient population (47 percent).
- Use of marketing research to help in feasibility studies (34 percent).
- Use of patient-oriented media advertising (20 percent).

As these percentages indicate, marketing techniques are being unevenly applied. Only nine percent of the administrators said they had ''formal'' marketing plans, but only six percent disagreed with the statement; ''Marketing is a legitimate function of hospitals''. Most hospitals do not have a formal marketing department for a good reason. Among physicians, hospitals' main customers, the word ''marketing'' is provocative, evoking a distasteful image of slick commercialism. ''Marketing'', in short, is a loaded word, often blocking rather than helping a hospital's survival efforts.

And yet, to survive, hospitals will be forced to rely on outside people, outside resources, and an outside image. Somehow hospitals must begin to see themselves from the point of view of their ''customers'' — physicians and the public. This task inevitably will require ''marketing techniques,'' whether we call them that or not, and money. How to do this — without third party support, without creating physician hostility, and without heating up community conflicts — remains unresolved, but will be a grist for a future editorial.

Richard L Reece MD

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Cover Painting
''Autumn Tranquility''

Dr. Claus A. Pierach is the artist of the cover painting. The farm belongs to a friend of his, a former fellow medical student, and is located in Wisconsin. Dr. Pierach had lost track of his friend after leaving Germany, and after many, many years his friend located Dr. Pierach, picking up their friendship where they had left off.

Dr. Pierach always carries his paints, brushes, etc. with him, and while visiting his friend, painted the cover artwork.

A native of Germany who came to the United States about ten years ago, Dr. Pierach is actively involved in the studies of hypertension and prophyria. He is an Associate Professor of Medicine of the University of Minnesota Teaching Unit at Abbott-Northwestern Hospitals, Minneapolis.

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Free Flap Reconstruction of the Lower Extremity

BRUCE L. CUNNINGHAM, M.D.,* WILLIAM W. SHAW, M.D.,† JACK K. MAYFIELD, M.D., MS.‡
and ALAN R. SHONS, M.D., Ph.D.#

Microvascular free flap transfers represent a valuable new technique for the reconstructive surgeon. An illustrative case is presented in which a free flap was used to reconstruct a lower extremity defect created by a dynamite blast.

THE ABILITY TO TRANSFER skin and its subadjacent subcutaneous tissue to reconstruct defects of the body surface has been the mainstay of plastic surgery. Considerable recent work has extended and refined techniques of flap transposition. The definition of flaps according to their vascular anatomy was a major step forward.[4,9] Random pattern flaps lack an anatomically recognized arterial-venous system and as such the flap is subject to the classic restrictions of length to width ratio and the necessity for delays. Axial pattern flaps contain at least one known axial vascular system and thus can be designed and transferred with a much longer length to width ratio than formerly thought possible.[11] The deltopectoral flap[1] and forehead flap[8] are examples of axial pattern flaps with a constant central arterial-venous system. Island flaps have a pedicle devoid of skin consisting only of the artery and vein. The mobility of an island flap is, of course, greater than a flap employing a skin base.

However, there are limitations in the use of skin flaps and not infrequently the surgeon is faced with problems insolvable employing conventional means. Responding to this dilemma several experimental projects were originated to determine the feasibility of elevating an island flap, isolating the 1mm nutrient vessel and reestablishing the vascular supply under the operating microscope at the recipient site. While early attempts were not met with uniform success the practicality of transferring the island flap as a free flap was established.[5,7,10]

This work culminated with the first successful transfer of a free flap from the groin to the lower extremity.[3] This clinical success heralded "the birth of a new era in reconstructive surgery".[2] Rapidly other centers report successful free tissue transfers for solution of a variety of surgical problems.

Currently the most commonly employed donor site is the groin. (Figure 1) An iliofemoral flap with a maximum dimension of 20 x 30cm can be elevated using the superficial epigastric or circumflex iliac artery and vein as the nutrient vessels.[10] Despite the size of this donor site, it can be closed primarily in most instances.

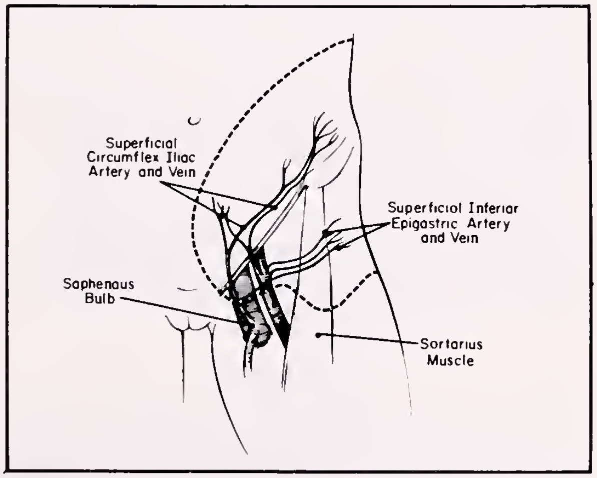
Superficial Circumflex Iliac Artery and Vein
Superficial Inferior Epigastric Artery and Vein
Saphenous Bulb
Sartorius Muscle

Fig. 1 — Anatomical basis of the groin flap. (Redrawn from Daniel, R. K., and Terzis, J. K., Reconstructive Microsurgery, Little Brown & Co., 1977, p. 216 by permission.)

The diameter of the artery is in the range of .8 to 1.5mm and the vein is slightly larger. These vessels can be approximated with a magnification of 10x or 16x employing a 10-0 monofilament suture material. The operation usually requires eight to 10 hours for completion and a total success of 80-90% is obtained in experienced hands. Post-op anticoagulants are not given as a rule.

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Complications consist of a partial or total loss of the free flap due to post-operative failure of the venous or arterial anastomosis. Despite this complication, the anastomosis can often be revised with salvage of the flap. In cases of partial skin loss the surviving subcutaneous tissue serves as an adequate base for split thickness skin grafting. Complications at the donor site are rare.

It is axiomatic that free flaps are inappropriate where split thickness skin graft or a local flap would suffice. At present free flaps are most commonly employed to reconstruct post-traumatic soft tissue defects of the extremity.[6] In certain instances free flaps are being used to reconstruct large soft tissue defects created at the time of a tumor resection.[12]

Free flaps offer several advantages over conventional flap techniques. Microvascular flaps are a one stage procedure where regional and cross leg flaps may require several stages. Following a free flap transfer the recipient site requires little or no immobilization. This has particular advantages in preventing joint stiffness and the hazards of thromboembolization seen with cross leg flaps. The donor site is frequently closed primarily and is more cosmetically acceptable than the donor site following a regional flap transfer.

Disadvantages in free flap reconstruction relate to the length of the initial procedure. The sacrifice of the recipient vessel may represent a hazard to extremities with compromised vascular supply secondary to trauma. However in most cases, the dual arterial supply to the extremity allows one to sacrifice an arterial branch without incurring a serious problem.

At the University of Minnesota we see a variety of complex reconstruction problems and have had the opportunity to employ free flaps on several occasions. We present a case report of the initial free flap done at the University of Minnesota.

Case Report

On December 25, 1977 a 20-year-old white male was flown to the University of Minnesota after sustaining multiple injuries in an accidental explosion of dynamite. His injuries included a below the elbow amputation of the left arm with multiple injuries of the fingers of the right hand. He had a comminuted grossly unstable open fracture of the right tibia and fibula with an 8cm tibial bone loss and massive soft tissue loss of the anterior compartment of the right leg. There were no ischemic changes of the right foot and posterior tibial pulses were felt. Anterior compartment musculature was absent but gastrocnemius, toe flexors and plantor sensation was intact.

Immediate surgical care consisted of debridement and dressing of his wounds. He required several subsequent debridements and revision procedures on the right hand and left arm stump. His right leg was debrided and placed in an external fixation device for

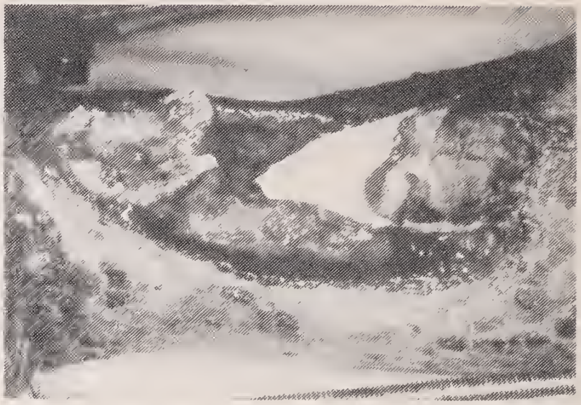

Fig. 2 — Soft tissue and tibial defect. The anterior tibial artery traverses the wound.

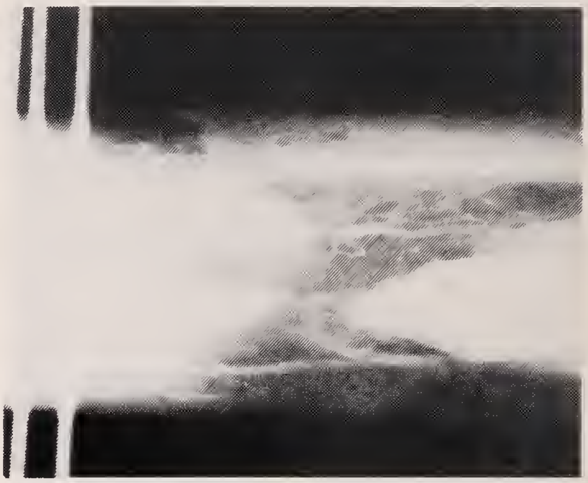

Fig. 3 — Arteriogram showing three vessel patency at level of defect.

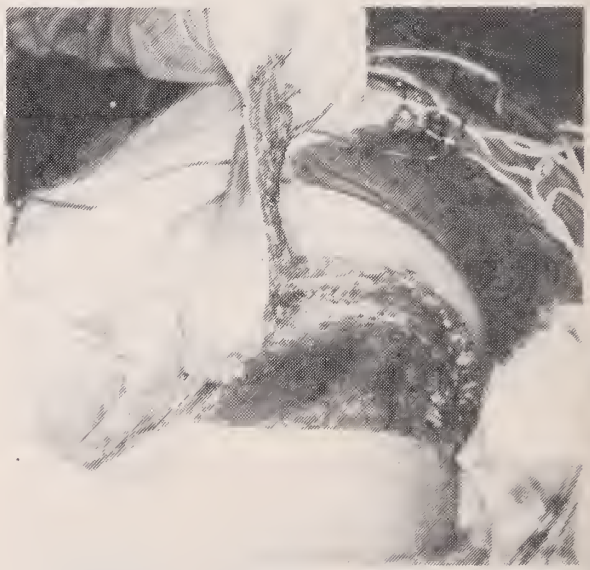

Fig. 4 — Free flap elevated demonstrating the vascular pedicle.

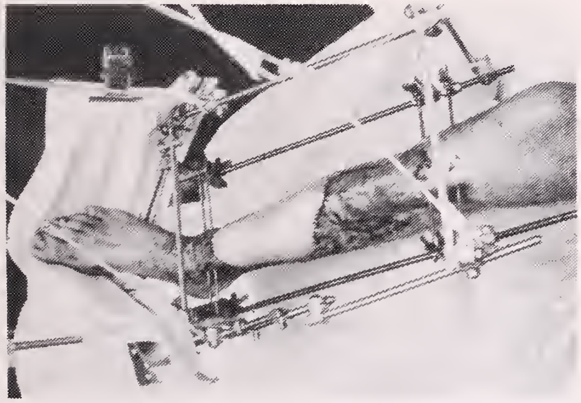

Fig. 5 — Postoperative view of leg with external fixation device in place.

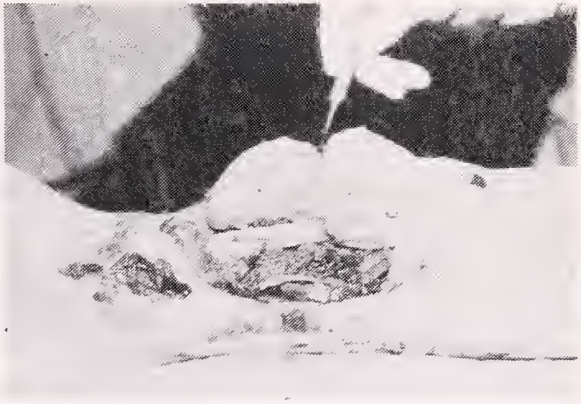

Fig. 6 — Edge of free flap elevated with bone grafts in place.

stabilization of the fracture. By January 11, 1978 most of the necrotic bone and tissue had been debrided from his right leg and it was possible to make an assessment of his condition. (Figure 2). The entire anterior compartment soft tissue was lost. There was a 10cm loss in the length of the tibia. The fibula was fractured at its distal portion, however there was no loss of length in that bone. Both bones were exposed in depth of the wound and the anterior tibial artery was intact and traversed the tissue defect. An arteriogram revealed three vessel patency at the level of the injury (Figure 3).

Because of the necessity for the external fixation device a cross leg flap would have been most difficult and in fact would not have provided adequate tissue for coverage due to the large area of loss. Split thickness skin grafting would have failed over the area of exposed bone and local muscle flaps were not feasible. The decision was made to transpose a groin flap into the area to be followed later by bone grafting of the tibial defect.

On February 9, 1978 he was taken to the operating room and an oval left groin flap measuring 14 x 21 cm based on the axis of the superficial epigastric and circumflex iliac arteries was elevated (Figure 4). The anterior tibial artery was dissected free and used as the recipient vessel. Under the microscope the common arterial trunk and two venous commitants were anastomosed. The donor site was closed primarily and drained. Postoperatively the patient received dextran. The flap showed good capillary fill and the margins healed rapidly (Figure 5). There were no complications.

On March 6, 1978 a 15cm section of fibula from the right leg was harvested and placed into the tibial defect by elevating an edge of the free flap (Figure 6). Cancellous bone chips from the iliac crest were also inserted into the bone defect. Solid fixation was obtained. He began partial weight bearing ambulation at the end of March. He was discharged April 12, 1978 in good condition ambulating with some assistance.

The technique of free flap transfer presents a useful solution to difficult problems in reconstructive surgery. The success of the procedure depends on a capable team approach and meticulous care with the microvascular anastomosis. In the future as experience with the technique is gained more widespread employment of the free flap to reconstruct a variety of defects can be expected.

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Arthroscopy of the Knee

Another Diagnostic Technique

JAMES D. PRIEST, M.D.*

When discussing arthroscopy of the knee, one is tempted to qualify it as a "new" idea, but it was conceived of and performed long ago. Professor Takagi of Tokyo is credited with the first attempt to view the interior of a knee joint with an endoscope in 1918, and Bircher published the first paper on this procedure in Germany in 1921.[1] Interest in arthroscopy of the knee has waxed and waned in this country during the intervening years, probably because the instruments lacked durability and accuracy.[2] However, in the past few years a number of satisfactory arthroscopes have become available, and interest is again increasing in this technique for the diagnosis of knee injuries.

Arthroscopy of the knee is a minor surgical procedure done under local or general anesthesia. It is performed in an operating room or an area in which sterile technique may be maintained, and is not considered an office procedure. Where, then, does arthroscopy fit in diagnosing knee disorders?

Arthroscopy and Arthrography of the Knee

History, physical examination, appropriate laboratory studies, and routine Xrays are primary sources of information for the examining physician. Arthrography of the knee is an Xray technique in which radio-opaque dye is injected into the joint. The dye outlines the two menisci, and may reveal tears within them. Arthrography contributes significantly to the information of the diagnosing physician, but as with any given technique, it has inadequacies. The course of the popliteus tendon and its sheath make the lateral meniscus difficult to view posteriorly on arthrography. Chondromalacia of the patella and erosion of articular cartilage on the femoral and tibial condyles are not well seen with arthrography. Disruption of the anterior or posterior cruciate ligament is difficult to ascertain with this technique. The medial meniscus, in contrast, is usually especially well demonstrated by the arthrogram.

Through the routine anterior approaches, the lateral meniscus is usually well visualized with the arthroscope, while the posterior horn of the medial meniscus is not. The synovial lining of the joint, the anterior cruciate ligament, the undersurface of the patella, and the medial and lateral tibio-femoral articulations are

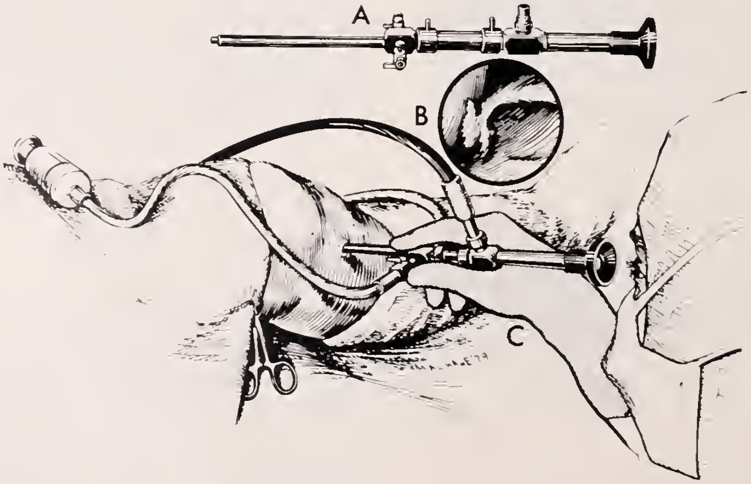

Figure — (A) The arthroscope, (B) A torn meniscus as seen through the arthroscope, (C) The operative field during arthroscopy of the knee.

This is the second of two articles by Dr. James Priest on the diagnosis of knee disorders. The first was published in the September 1979, issue of *Minnesota Medicine*.

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usually well visualized by the arthroscopist.

The two diagnostic techniques of arthrography and arthroscopy are not mutually exclusive, but actually complement each other. In addition, both procedures are safe, with few reported complications. Arthrography involves less time and expense, while arthroscopy may yield more overall information about the joint.

When, then, should each of these techniques be applied? This question is not easily answered, is open to considerable controversy, and must be answered by each examining physician for himself. Ligament injury is probably best diagnosed by physical examination, but when internal derangement of the knee is suspected and not accurately discernible by history, examination, and routine Xrays, arthrography and/or arthroscopy may be advised.

Arthroscopy as a Diagnostic Technique

The arthroscope has been found in recent years to be an excellent diagnostic tool. Pevey showed the overall accuracy of clinical examination to be 71.8 percent, of arthrography to be 84.3 percent, and of arthroscopy to be 90 percent.[3] In 100 patients with knee derangement, DeHaven and Collins found clinical diagnosis correct in 72 percent, arthrography for meniscus tears accurate in 78 percent, and arthroscopy correct in 94 percent.[4] Hirschowitz revealed the accuracy of clinical diagnosis to be 72 percent, arthrography 77 percent, arthrotomy 80 percent, and arthroscopy 94 percent.[5] Dandy and Jackson made a study of the impact of arthroscopy on the management of disorders of the knee. Of 614 knees which would have been operated upon had arthroscopy not been available, open operation was avoided in 32 percent and a different operation was done or planned in 27 percent.[6] Ewing and Mahon, in a similar study, found that in 150 patients who underwent arthroscopy, 32 percent were spared unnecessary surgery, and in 42 percent the diagnosis was altered through use of the arthroscope.[7] The orthopaedic literature, then, supports use of the arthroscope as a diagnostic tool.

Technique of Arthroscopy

Arthroscopy is performed under sterile conditions. A small incision is made over the anterolateral aspect of the knee joint, and the arthroscope is inserted into the joint. A fiberoptic light cord and separate tubes for the inflow and outflow of sterile saline are attached to the arthroscope. The joint is infused with saline so that the tip of the arthroscope and the view of the examiner are not obstructed by synovial or other tissues. The patient's extremity is supported and positioned by an assistant throughout the procedure.

With the examination beginning in the suprapatellar pouch region, the synovial lining is usually well visualized. Chondromalacia of the patella is seen as small frond-like projections or filmy, translucent excoriations of cartilage hanging from the undersurface. The medial femoral condyle can be followed from the patello-femoral joint distally, and may reveal damage, even ulceration of cartilage, over its weight bearing surface. The anterior two-thirds of the medial meniscus are usually well visualized, but the posterior corner of this cartilage is usually not seen from an anterior approach. Only when ligament laxity allows unusual separation of the joint surfaces, or when a posterior arthroscopic puncture is made, is the posterior horn of the medial meniscus well seen. Unless overgrown by synovial tissue, the anterior cruciate ligament may be well examined. The lateral femoral condyle and lateral meniscus are usually well seen. In contrast with arthrography, the posterior portion of the lateral meniscus is usually seen clearly at arthroscopy.

Following the procedure, saline is evacuated from the joint and the arthroscope is withdrawn. Usually a single suture closes the incision and a band-aid is applied. A patient may be active, even participate in athletics within a few days after the procedure.

Other Arthroscopic Instrumentation

A small probing instrument can be placed into the joint through a separate tiny incision as an aid in diagnosing meniscal or cruciate ligament tears. This instrument is used to palpate the internal features of the joint and sometimes proves invaluable in revealing pathology. Small biopsy forceps and grasping instruments are used on occasion. Use of this type of instrument has, in fact, heralded the beginning of a new concept and perhaps a new era in orthopaedic surgery, that of arthroscopic surgery. It is presently possible with cutting and grasping instruments to remove loose bodies or torn portions of a meniscus from the knee joint through tiny incisions, avoiding the necessity of open operation.

Expertise Required in Arthroscopy

Finally, while the procedure of arthroscopy of the knee might appear to be simple, it is in fact a difficult one to master. It is a demanding technique requiring practice and repetition. Experience is necessary for interpretation of both normal and abnormal findings. It has been estimated that between 50 and 100 procedures must be performed before an arthroscopist feels confident in his findings. The arthroscope is not an instrument for occasional use, and is probably best left in the hands of the orthopaedic surgeon.

Summary

Arthroscopy is a diagnostic technique for knee disorders which has proven to be effective. This procedure may be utilized where history, examination, and Xrays are not entirely diagnostic. In the future, it is possible that arthroscopy will be used not only for diagnosis, but also in surgical management of the injured knee.

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Variant A-V Block Secondary to Concealed Conduction

KYUHYUN WANG, M.D., F.A.C.C.* and DAVID A. BERMAN, M.D., F.A.C.P., F.A.C.C.*

Interesting consequences of concealed conduction are described in two patients. In one patient, concealed retrograde conduction from ventricular premature beats resulted in a variant Wenckebach phenomenon. In the second patient, concealed junctional premature beats resulted in apparent 2:1 A-V block. Unexplained PR prolongation and non-conducted P waves should raise the possibility of this condition.

CONCEALED CONDUCTION is an important concept in the understanding of many arrhythmias.[1] It can result in varied and complicated arrhythmias. This paper describes interesting consequences of concealed conduction in two patients.

Case Report

Case 1

In this patient with prolapsing mitral valve leaflets, multiple interpolated ventricular premature beats (VPBs) are evident in the rhythm strip (Figure 1a). Concealed retrograde conduction from these VPBs to the A-V (atrio-ventricular) junction renders the latter partially refractory and the PR intervals of subsequent sinus beats are prolonged. In Figure 1b, three consecutive interpolated VPBs with concealed retrograde conduction to the A-V junction cause the subsequent sinus beats to be conducted to the ventricle with progressively longer PR intervals until one is completely blocked (variant Wenckebach phenomenon.)

Case 2

This patient with no known cardiac disease (Figure 2a) has frequent A-V junctional premature beats (JPBs) (R3, R8) with retrograde conduction to the atrium (P_3, P_9). Occasionally, inverted P waves are seen without an accompanying QRS (P_5, P_{11}). The R_4-P_5 and R_9-P_{11} intervals are identical to the R_2-P_3 and the R_7-P_9 intervals suggesting that P_3, P_5, P_9 and P_{11} are elicited by the same mechanism, namely JPBs. Some JPBs are conducted only to the atrium and not to the ventricle (concealed conduction). The reason for the failure of these beats to capture the ventricle is that they follow a long RR cycle created by the previous JPBs (R_3 and R_8) and occur during the lengthened refractory period of the preceding sinus beats (Ashman's phenomenon).

In the rhythm strip immediately following (Figure 2b), a JPB (R_{14}) is not conducted to the atrium because the latter has already been activated by a sinus impulse and the P wave (P_{16}) is upright instead of being negative as in Figure 2a (A-V dissociation). Non-conducted P waves (P_{18}, P_{20}, P_{22}) are most likely due to concealed JPBs. Each JPB after the first one (R_{14}) occurs during the lengthened refractory period of the preceding sinus beats related to the longer preceding RR cycle and, therefore, fails to capture the ventricle (concealed conduction). These JPBs, unlike those in Figure 2a, are completely concealed and are not propagated to either the atrium or the ventricle. These impulses, however, affect subsequent beats (P_{18}, P_{20} and P_{22})

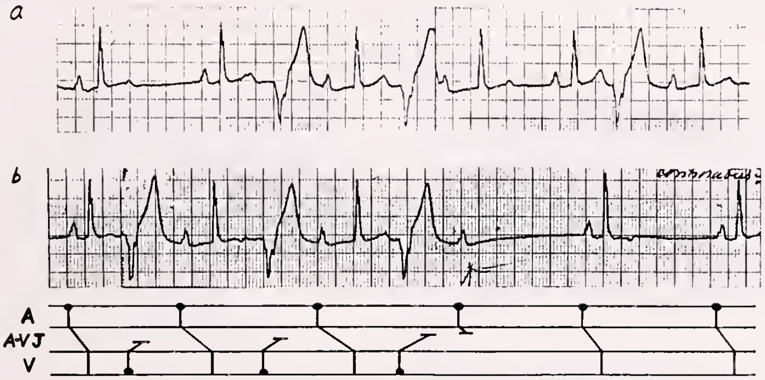

Fig. 1 — Case 1 — see the text for interpretation. A: atrium, AV-J: atrioventricular junction, V: ventricle.

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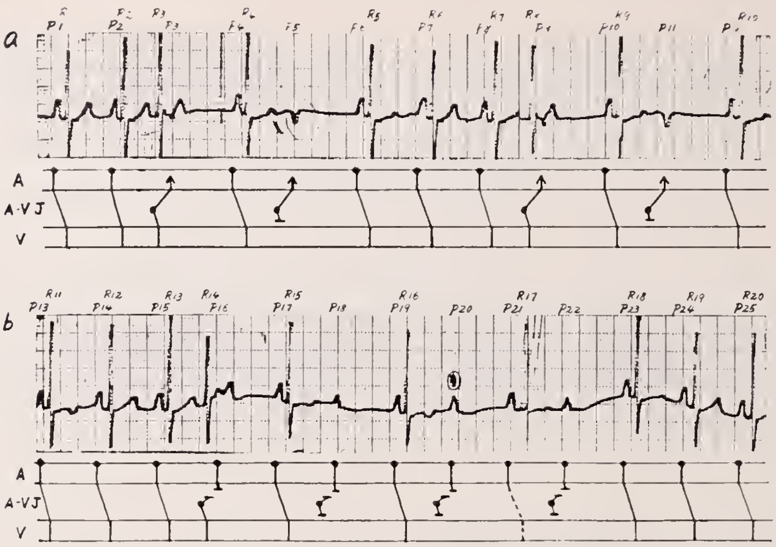

Fig. 2 — Case 2 — see the text for interpretation. Post extrasystolic T wave changes are evident. R: QRS, P: P waves, A, AVJ, V: as in Figure 1, (R_{17} is not registered due to failure of the recording machine.)

by making the A-V junctional tissue refractory and result in apparent 2:1 A-V block. These deductions are based on the observation of conducted JPBs in the same patient (R_3, R_8 and R_{14}).

Discussion

Concealed conduction implies partial penetration of the A-V junctional tissue by an impulse arising from the atrium, ventricle, or A-V junction in the absence of A-V block. The impulse fails to emerge in the atrium, ventricle, or both depending upon the direction of propagation. Since the A-V junctional depolarization is not registered on the conventional ECG, it is "concealed." This concealed conduction affects the formation and conduction of the subsequent impulse by rendering the conduction tissue refractory. It is through this alteration of subsequent impulse formation or conduction that the presence of concealed conduction can be inferred from conventional ECG.

Langendorf and coworkers[2] described patients in whom first and second degree A-V block, alternating PR intervals,[3] and pseudo-Wenckebach phenomenon[4] were believed to be due to concealed A-V junctional premature beats. This mechanism was subsequently proven by His bundle electrography by Rosen and colleagues.[5] Unexplained PR prolongation and non-conducted P waves should raise the possibility of this condition.

Concealed conduction and its effect on the subsequent impulse are due to physiologic refractory period of the conduction system. The role of physiologic properties of the conduction system in the ultimate manifestation of arrhythmia has been emphasized.[6]

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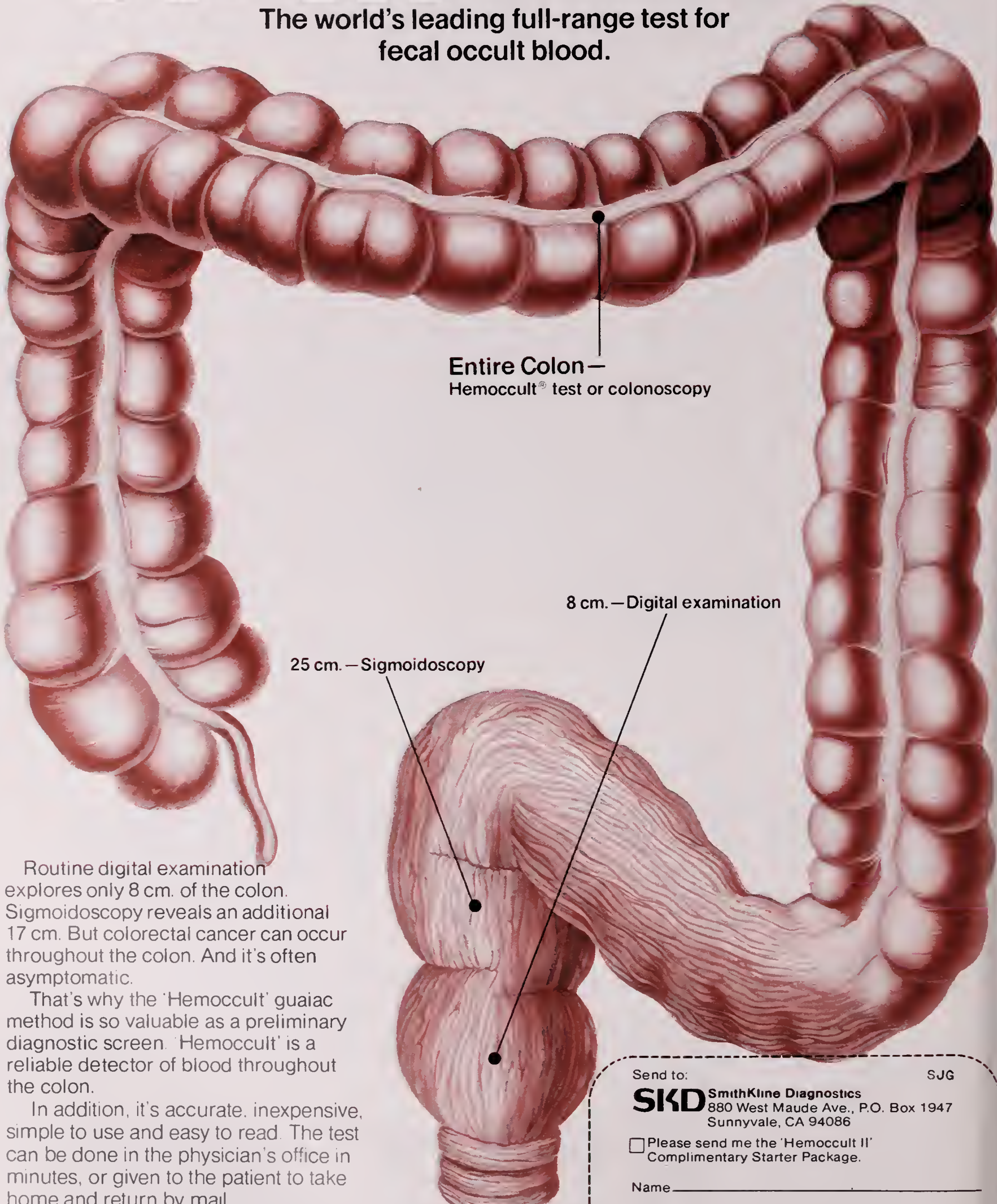

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Ergot Induced Unilateral Brachial Arterial Occlusion

DAVID R. DEMARTINI, M.D.;* MILTON W. PLUCKER, M.D.;* FRANK JOHNSON, M.D.;†
and FREDARICK L. GOBEL, M.D.‡

A 61-year-old farmer presented with severe pain and weakness in the left arm due to ergot-induced unilateral brachial artery occlusion. At arteriography the obstruction was abrupt, suggesting thrombotic occlusion. When the obstruction persisted for three days following drug withdrawal, surgery was performed. Arteriography ten days following surgery demonstrated a patent saphenous vein bypass graft and a normal left brachial artery.

ERGOT INTOXICATION may lead to occlusion of a peripheral artery angiographically simulating occlusion due to a thrombus or atherosclerosis. Such arterial spasm may even occur with small amounts of ergot and may persist for days after withdrawal of the drug. Any artery and extremity may be involved.

The opportunity to study a patient with ergot-induced unilateral brachial artery occlusion which persisted for several days following withdrawal of the drug, prompted this report.

Case Report

A 61-year-old farmer suffered from migraine headaches since age 12. He began using ergotamine to prevent these attacks in 1970.

In November, 1976 the patient suffered constant severe aching in both shoulders and the upper back, progressing into both forearms. By February, 1977 a burning pain in the left hand had developed. He noted that his left hand was so weak and painful that he could no longer perform his farm work and, on one occasion, fell from a ladder due to weakness in the left hand. The patient also complained of several episodes of resting chest pain suggestive of myocardial ischemia.

He had not experienced trauma to his left arm. The patient also had mild diabetes mellitus controlled by diet and an Xray demonstrated duodenal ulcer which healed during medical therapy.

On admission to the hospital the blood pressure was 140 mm Hg systolic and 90 mm Hg diastolic in the right arm. The pulse rate was 84 beats per minute. The left forearm was cyanotic and the fingers of the left hand were cool. There were no pulses in the left arm distal to the left axillary artery pulsation, which was normal. After opening clenched fists capillary filling of the left hand occurred approximately 45 seconds later than the right hand. A fourth cardiac sound was present. Although he appeared to be euthyroid a multinodular

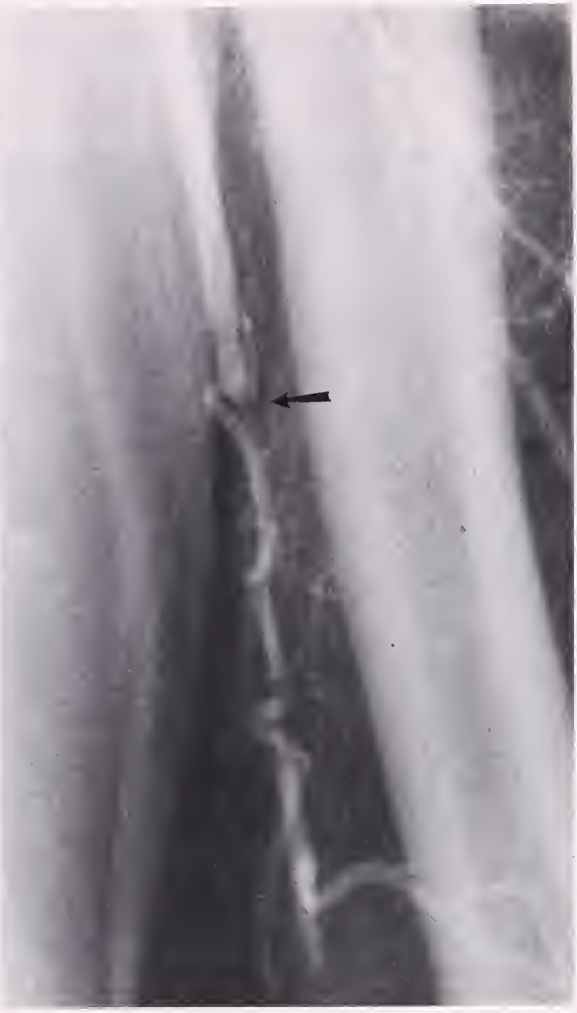

Fig. 1(A) — An arteriogram demonstrates complete and abrupt occlusion of the brachial artery at the mid humerus, suggesting thrombotic obstruction (arrow).

---

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†Cardiovascular surgeon, Minneapolis and President, Minnesota Medical Association.

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thyroid gland was palpated. A grade ii/vi systolic ejection murmur was present at the left sternal border.

The laboratory data included a hemoglobin of 14.0 gm%, and a normal platelet count. The electrocardiogram and chest x-ray were both normal. Thyroid function studies were also normal.

An arteriogram demonstrated complete occlusion of the brachial artery at the level of the mid-humerus (Figure 1A). The artery gradually narrowed to a point where it ended abruptly simulating a thrombotic occlusion. After 0.8 mg of sublingual nitroglycerin the diameter of the brachial artery doubled proximally but the obstruction remained complete. The left and right coronary artery contained only mildly obstructive disease. A left vertebral artery arose anomalously from the arch of the aorta and tapered to complete occlusion approximately 3-4 cm. from its origin.

The patient was unable to give an accurate history of ergot ingestion. His pharmacist supplied the information that the patient had purchased a considerable quantity of ergot (Figure 2). Assuming consumption of all of these tablets he averaged 27 mg of ergot per week during the year prior to admission.

Ergot was withdrawn on hospital admission and by 48 hours some improvement in the filling time of the left hand was noted. After 96 hours the pulse remained absent. Since we could not exclude the presence of a thrombotic occlusion we elected to surgically bypass the obstructed artery. At surgery the site of obstruction was not seen. A saphenous vein graft was anastamosed from the brachial artery to the radial artery. Thereafter a palpable left radial pulse was present. Following surgery the capillary filling time in the left hand was similar to that of the right hand.

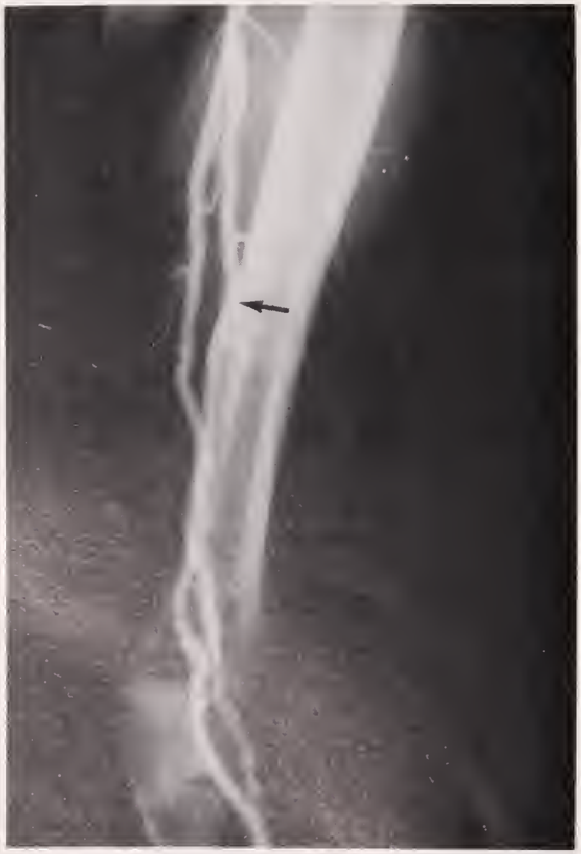

Fig. 1(B) — A post operative arteriogram demonstrates a patent saphenous vein graft and a patent brachial artery. The site of previous obstruction is indicated by an arrow.

Ten days following surgery a repeat arteriogram revealed a patent saphenous vein graft and a patent brachial artery. The previously demonstrated brachial artery obstruction was no longer present (Figure 1B).

Discussion

Unilateral brachial artery spasm with obstruction following oral ergot therapy is unusual and reported cases have usually been associated with administration by rectal suppository.[1] When arterial spasm occurs following ergot therapy, symmetrical involvement, usually the lower extremities, can be expected; however, isolated mesenteric, renal and coronary artery spasm have also been noted.[2–4] The mechanism whereby isolated vessels are selected for involvement in this vasospastic process is not clear.

Although most instances of clinical ergot toxicity have been associated with a dosage in excess of the recommended amounts (6 mg. orally or 4 mg. rectally each day but not to exceed 10 mg. per week), serious ischemic episodes have been associated with as little as 2.5 mg. of ergotamine tartrate.[4] The patient reported had used two and a half to six times the recommended weekly amount (Figure 2).

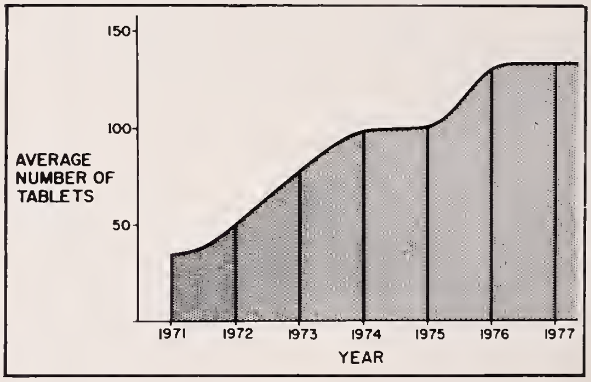

Fig. 2 — Average intake of ergot since 1971.

Persistence of arterial spasm and symptoms following drug withdrawal have been previously emphasized.[5] Complete resolution has been noted as soon as 24-hours following cessation of drug usage[6] and as long as eight days.[7] The onset of clinical toxicity has also been delayed as long as three days after withdrawal of ergot therapy.[7] Lack of appreciable improvement within three days in this case would not seem unusual in light of reported cases.

Angiography usually reveals intense arterial spasm, manifested by smooth narrowing of the vascular lumen. On occasion, as in this case, there may be sudden obstruction of the vessel mimicking thrombotic occlusion. Indeed, thrombosis has frequently been associated with ischemia to limbs secondary to intense arterial spasm induced by ergot. It was this appearance that lead us to believe that the obstruction was secondary to a thrombus. Although we cannot be certain that a thrombus was not present initially and then subsequently dislodged, the smooth vascular wall and absence of peripheral obstruction render arterial spasm most likely to be the mediator of obstruction. In addition a biopsy from the brachial artery at the time of surgery was normal.

Although drug withdrawal is the most effective and important part of therapy, other adjunctive methods have also been employed, including heparin, hyperbaric oxygen, low molecular weight dextran, surgical and chemical sympathectomy, and intravascular vasodilator therapy. Recently nitroprusside has been found to be effective in reversing ergot-induced arterial spasm in two patients with bilateral lower extremity ischemia.[8] In the patient reported 0.8 mg. sublingual nitroglycerin was not effective in relieving the obstruction although there was dilation of the diameter of the proximal vessel by approximately 50%.

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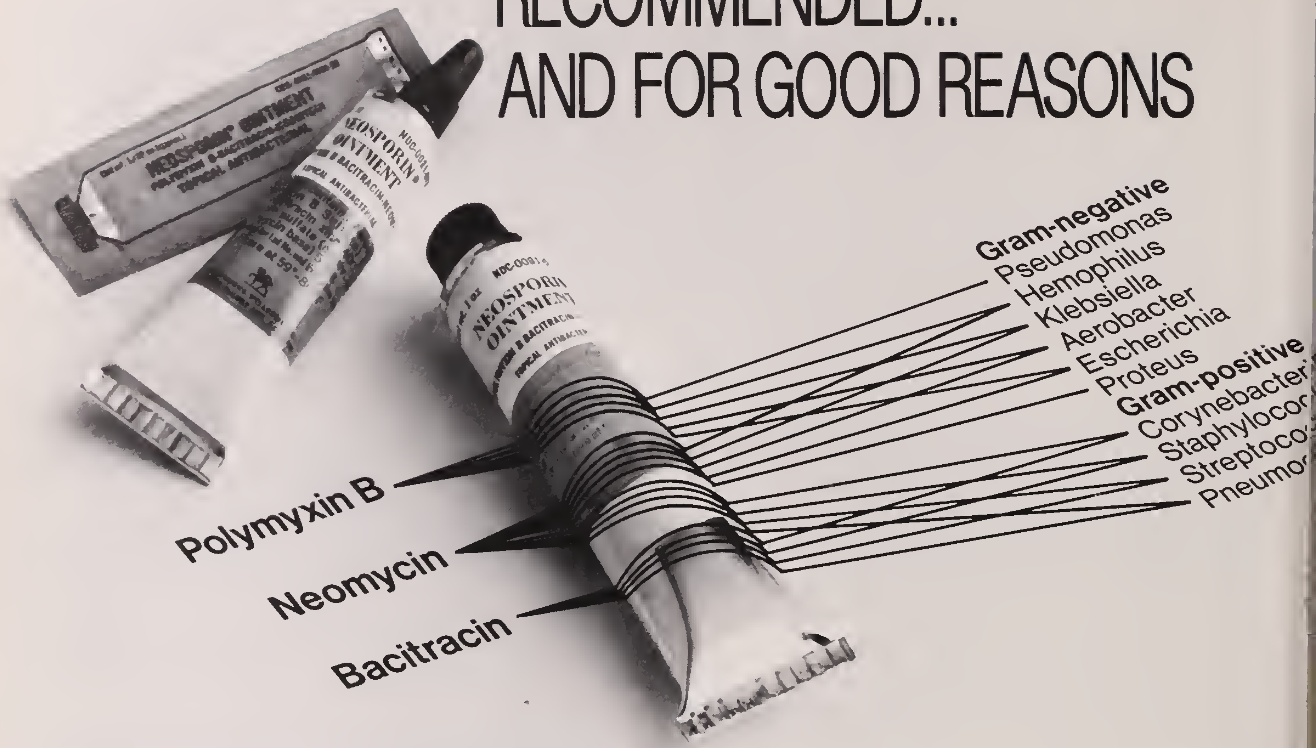

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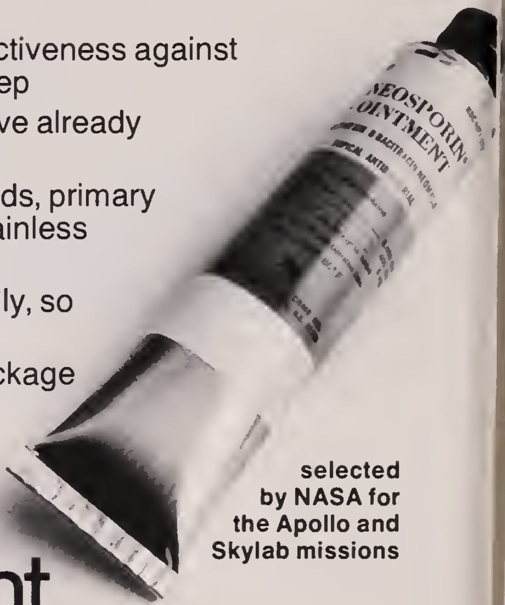

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Left Atrial Myxoma Presenting as Shock

Diagnosis by Echocardiography

RICHARD W. ASINGER, M.D.;* WILLIAM E. STRAUSS, M.D.;* MORRISON HODGES, M.D., FACC;*
TERRY ROURKE, R.D.M.S.* and HOVALD K. HELSETH, M.D.*

A patient presented with systemic hypotension associated with elevated right and left sided filling pressures, metabolic acidosis, and oliguria which progressed to anuria. The cause of the hypotension was not evident on initial evaluation although the clinical presentation supported obstruction of blood flow. An echocardiogram was performed on an urgent basis, and revealed a proplapsing left atrial myxoma. Surgical removal of the tumor was successful. Without urgent echocardiography, the diagnosis probably would not have been made antemortem.

THE PRESENTING SIGNS and symptoms of left atrial myxoma are protean,[1] and include systemic embolization, obstruction at the mitral valve level, or constitutional symptoms.[1] The patient described here presented with shock, without an obvious cause although clinical evidence of elevated right and left sided filling pressures were consistent with intracardiac obstruction of blood flow. The diagnosis of left atrial myxoma was made by echocardiography. Because of the severity of the patient's acute illness, we doubt that the diagnosis would have been made without this method of examination.

Case Report

A 55-year-old white male was brought to the emergency room because of progressive shortness of breath of 10 days duration, a nonproductive cough, and pedal edema. The dyspnea was less in the supine position. He had noted dyspnea on exertion over the past year, and had had one episode of pedal edema which spontaneously resolved. He had not had syncope, chest pain, or symptoms of peripheral arterial emboli. He gave a history of high alcohol intake with very heavy drinking for several months prior to admission.

Physical examination revealed an anxious but oriented man who was dyspneic at rest. No peripheral blood pressure could be obtained with the cuff method. He was cyanotic and his skin was mottled, cool, and moist. The apical heart rate was 125 per minute and irregularly irregular. The carotid and femoral pulses were present but no other pulses could be felt in the upper or lower extremities. The jugular veins were distended to the angle of the jaw at 45 degrees elevation. Coarse expiratory rhonchi were present over the lower lung fields. The heart sounds were distant with an early low frequency diastolic sound present at the apex. No murmurs were heard. The abdomen was distended with evidence of ascites; the liver span was 15 cm on percussion. There was 3+ pitting edema of the lower extremities to the level of the anterior iliac crests.

An electrocardiogram showed atrial fibrillation with a ventricular rate of 125 beats per minute. Electrocardioversion was successful after which there was a sinus tachycardia of 125 beats per minute, right axis deviation, and the suggestion of left atrial enlargement or "overload". A chest x-ray showed enlargement of the heart, increased pulmonary vascularity and small bilateral pleural effusions. Arterial blood gas analysis revealed a pO_2 of 89 mmHg, a pCO_2 of 18 mmHg, and a pH of 7.30. A central arterial catheter was placed and revealed a systolic pressure of 65 mmHg. With dopamine administration a systolic pressure of 90-100 mmHg was maintained. A catheter was positioned in the pulmonary artery; the pressure was

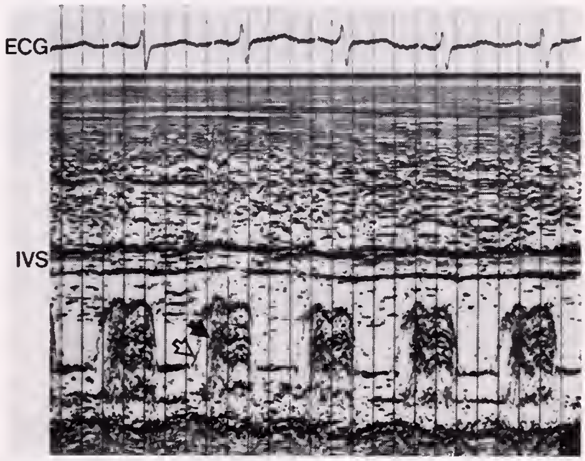

Fig. 1 — Echocardiogram of mitral valve in our patient, recorded pre-operatively. IVS — interventricular septum. Open arrow indicates the anterior mitral valve leaflet, closed arrow indicates the prolapsing tumor with characteristic layered echoes posterior to the anterior mitral valve leaflet. Note the early diastolic echo-free space between the anterior mitral valve leaflet and the prolapsing myxoma.[11]

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*Cardiology Sections and Departments of Medicine, and the Cardiovascular Surgery Section, Department of Surgery, Hennepin County Medical Center and the University of Minnesota, Minneapolis, Minnesota.

Presented at the May, 1977 meeting of the Minnesota Society of Internal Medicine in Minneapolis, Minnesota.

Address for reprints: Richard W. Asinger, M.D., Cardiology Section, Department of Medicine, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, Minnesota 55415.

55/22 with a mean of 38 mmHg. The patient's condition deteriorated; the metabolic acidosis was persistent and required intravenous bicarbonate. Urine output progressively decreased to anuria despite large doses of intravenous furosemide. An echocardiogram was obtained approximately 12 hours after admission, primarily to evaluate the possibility of pericardial effusion. The echocardiogram revealed the characteristic echoes of a left atrial myxoma behind the anterior mitral valve leaflet in diastole (Figure 1).

We felt that emergency surgical intervention to relieve left ventricular inflow obstruction was indicated, although we realized there would be an increased risk during induction of general anesthesia.[2] Institution of partial cardiopulmonary bypass under local anesthesia allowed the discontinuation of dopamine and maintenance of a systolic aortic pressure of 100 mmHg prior to the induction of general anesthesia. Under subsequent general anesthesia, a median sternotomy was performed and complete cardiopulmonary bypass instituted. The left atrial myxoma and the portion of the interatrial septum surrounding the fossa ovalis were removed via the right atrium, using a transseptal approach. The mitral valve apparatus including the chordae tendineae was intact. In the immediate post-operative period, the left atrial pressure was 6 mmHg and the central arterial pressure (unsupported) was 110/70 mmHg. A diuresis occurred following surgery with a loss of 7 kg in three days. The post-operative period was complicated by recurrent atrial arrhythmias and right sided empyema, but he had made a complete recovery five weeks after operation. An echocardiogram 14 days after surgery demonstrated normal mitral valve motion (Figure 2).

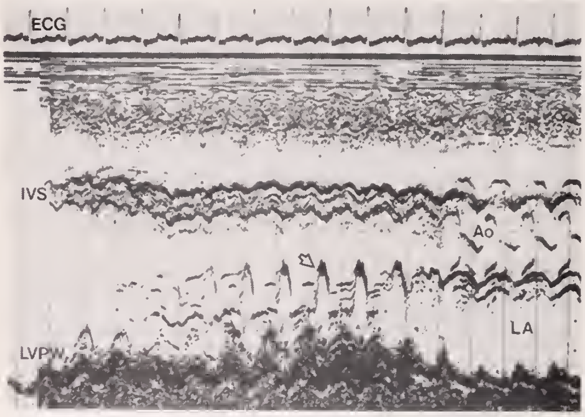

Fig. 2 — Echocardiogram of our patient recorded 14 days post-operatively demonstrating a continuous M-mode sweep from the body of the left ventricle to the aorta. Imaged structures include: Ao — aorta, LA — left atrium, IVS — interventricular septum, LVPW — left ventricular posterior wall, and the open arrow indicates anterior mitral valve leaflet. There is no evidence of residual left atrial myxoma.

Discussion

Left ventricular inflow obstruction by a left atrial myxoma may mimic mitral stenosis. Intermittent obstruction may lead to syncope, shock, or sudden death.[1,3-6] Our patient presented with a clinical picture of severe heart failure, and hypotension. The etiology was not apparent on initial evaluation. A massive pulmonary embolus was considered but this diagnosis was not supported by the arterial pO_2 of 89 mmHg and the history of progressive clinical symptoms. In addition, no clinical evidence supported a diagnosis of acute myocardial infarction. Obstruction to blood flow through the heart, causing decreased peripheral perfusion and elevated right and left sided filling pressures seemed the most likely pathophysiologic mechanism. The possibility of a pericardial effusion prompted us to obtain an echocardiogram. The diagnosis of left atrial myxoma as the obstructing lesion was supported by the relatively rapid clinical course, positional changes in symptoms, and the severity of obstruction to blood flow. Patients with left atrial myxomas with this presentation should be considered unstable. This situation is often associated with an unfavorable prognosis.[1-6]

The diagnosis of left atrial myxoma in our patient was established by echocardiography. Past reports have documented the efficacy of echocardiography in the diagnosis of left atrial tumors, and stressed that further documentation by angiography may not be necessary.[7-10] In our patient, the echocardiogram (Figure 1) demonstrated the characteristic dense parallel echoes posterior to the anterior mitral valve leaflet in diastole. An echo-free space separating the opening of the anterior mitral valve leaflet from the prolapsing myxoma was also present.[11] The tumor could also be detected in the left atrium throughout the cardiac cycle in the area of the atrioventricular junction. We felt that further documentation of the tumor by angiography was unnecessarily risky and time consuming considering the urgency of the clinical situation. Therefore the patient was taken directly to the operating room.

This case demonstrates that echocardiography can reliably support the diagnosis of left atrial myxoma in a patient with severe life threatening left ventricular inflow obstruction. Angiographic documentation may not be necessary. Most patients with left atrial myxoma do not present as seriously ill as our patient, and it is possible that our patient's alcoholism contributed to his delayed presentation. Nevertheless, left atrial myxoma should be considered in patients with hypotension of unknown etiology particularly if associated with elevation of right and left sided filling pressures; in these patients echocardiography can rapidly point to the diagnosis.

Acknowledgments

We wish to thank Dr. Howard B. Burchell for his advice and review of this manuscript. Ms. Barbara Nelson provided secretarial services.

References will be found on page 744

Limbitrol — A Medical Dream or Nightmare

THEODORE G. LARSON, M.D.*

Limbitrol is a new combination drug which is promoted for the treatment of moderate to severe depression with anxiety. Some potential hazards of Limbitrol therapy are discussed.

LIMBITROL IS A NEW combination drug containing the minor tranquilizer chlordiazepoxide (Librium) and the tricyclic antidepressant amitriptyline (Elavil, Endep). It is marketed in tablet form containing the ratio 10 mg. chlordiazepoxide to 25 mg. amitriptyline. The drug is promoted for the treatment of moderate to severe depression with anxiety with a suggested dose range of three to six tablets daily. Available information indicates that studies of Limbitrol have been limited to short-term therapy.[1]

On paper the combination of a proven antidepressant with a proven antianxiety drug should be an ideal drug. Let's consider the actual use of Limbitrol in the treatment of depression. The usual plan for tricyclic anti-depressant treatment of depression[2] involves three to six weeks' time to establish a fully therapeutic dose. Starting with 25 mg. amitriptyline q.i.d. the dosage is increased gradually to an effective optimal drug dose. Usually this amounts to about 150 mg. amitriptyline per day but may require up to 300 mg. per day.

After optimal dose is reached, that dose is continued for three or four months. Then gradual reduction of the dose is instigated. Some patients manage to discontinue medication in six months, others require a maintenance dose for several more months. Some require indefinite continued drug treatment.

Using Limbitrol with a ratio of 10 mg. chlordiazepoxide to 25 mg. amitriptyline, the average daily dose of chlordiazepoxide would be 60 mg. for at least three to four months. In some cases, the daily dose could be as high as 120 mg. chlordiazepoxide.

Chlordiazepoxide is well known for producing physical and psychological dependence as are most sedative medications.[3] It seems highly probable that chlordiazepoxide dependence will occur in a certain percent of patients treated with Limbitrol. The patient who is physically dependent on chlordiazepoxide may have great difficulty lowering his dose of Limbitrol. Even gradual withdrawal of chlordiazepoxide or other sedatives can produce severe discomfort; anxiety, tremors, insomnia, possibly seizures.[3] Although the patient's depression may have subsided and he no longer needs amitriptyline, he still may "need" chlordiazepoxide to satisfy an iatrogenic drug dependency — a true nightmare for the patient and the physician.

The potential hazards of Limbitrol therapy appear to be:

1. Iatrogenic drug addiction albeit unintentional on the part of the physician or the patient.
2. Abrupt withdrawal of sedatives such as chlordiazepoxide can result in serious risk to the patient — delirium, convulsions, even death can result in the dependent patient.[3-5] Abrupt withdrawal can occur for a variety of reasons: patient may lack money for medication; he may lack a valid prescription; or even the patient's sudden whim to "stop everything."
3. Overdose in depressed patients is all too common. The potentiation of chlordiazepoxide sedation by amitriptyline could be far more hazardous than an equal dose of either drug alone.
4. The side effects of amitriptyline may prevent blatant abuse of Limbitrol. However, the addictive person may be willing or able to tolerate high doses of the drug. This patient could be in serious physical danger due to toxic drug serum levels. Cardiac dysrhythmia and arrhythmia are known toxic effects of amitriptyline.[2]

The main intent of this discussion is to raise serious question about the long-term daily use of a drug combination containing an addictive minor tranquilizer.

It must be emphasized that successful treatment of depressions requiring tricyclic antidepressants usually involves long-term therapy. It does not seem medically wise to use Limbitrol for these patients.

---

*Medical Director, Northern Pines Mental Health Center, Inc., Little Falls, Minnesota.

If Limbitrol is prescribed for these patients, it is recommended that its use be strictly limited to three to four weeks. The patient should then be switched to tricyclic antidepressant medication alone. If anxiety continues to be a symptom it is suggested that a major tranquilizer be substituted for chlordiazepoxide.

Why not use a major tranquilizer initially with a tricyclic antidepressant and avoid possible drug dependence? There is a wide variety of effective major tranquilizers, especially phenothiazines, which do not have any problem with drug dependency.

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Dr. Robert Priest receives Bolles-Rogers Award

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Shock Lung: An Overview

MICHAEL A. HARRIS, M.D.*

The term Shock Lung describes an entity of progressive pulmonary insufficiency in patients with major body trauma or decrease in tissue perfusion. The incidence, etiology, clinical manifestations, differential diagnosis, pathology and treatment are reviewed.

SHOCK LUNG SYNONYMS include traumatic wet lung, congestive atelectasis, stiff lung, and hyaline membrane disease in the adult. Other names used in the literature to refer to this entity are seen in Table 1.

TABLE 1

Synonyms for Respiratory Distress Syndrome of Shock and Trauma
Adult hyaline membrane disease
Adult respiratory insufficiency syndrome
Bronchopulmonary dysplasia
Congestive atelectasis
DaNang lung
Fat embolism
Hemorrhagic atelectasis
Hemorrhagic lung syndrome
Hypoxic hyperventilation
Oxygen toxicity
Post-perfusion lung
Post-transfusion lung
Post-traumatic atelectasis
Post-traumatic pulmonary insufficiency
Progressive pulmonary consolidation
Progressive respiratory distress
Pulmonary edema
Pulmonary hyaline membrane disease
Pulmonary microembolism
Pump lung
Respiratory lung
Respiratory insufficiency syndrome
Shock lung
Stiff lung syndrome
Traumatic wet lung
Transplant lung
Wet lung
White lung syndrome

Review of the literature in the 1950s reflects little awareness on the part of clinicians of the significance of *respiratory failure after shock and trauma* and little or nothing appears from Korean War reports. During the Vietnam conflict, new problems were recognized and interest in the study of shock was revived by the challenge of war injuries. Rapid evacuation and prompt *fluid resuscitation* resulted in survivals from injuries that previously were fatal. The term "Shock Lung" was introduced during the Vietnam War to describe progressive pulmonary insufficiency in patients with major thoracic or nonthoracic trauma which *leads* to death frequently within hours to several days thereafter. The patients who succumbed most rapidly were those with multiple body trauma. In 1967, Ashbaugh recognized the significance of respiratory failure in civilian trauma and he coined the term "Adult Respiratory Distress Syndrome" (ARDS).

Patients with shock lung syndrome are unable to oxygenate blood effectively, even those with lungs not traumatized. Hypoxemia (PaO_2 less than 75 mm Hg) often exists even though no signs or symptoms of respiratory insufficiency exist. Once the signs and symptoms of respiratory failure become manifest, the pathologic changes in the lungs are relatively far advanced and difficult to revert to normal. For these reasons, shock lung syndrome should be suspected on purely clinical grounds in all patients sustaining any type of severe body trauma.

However, multiple causes of respiratory insufficiency may be present simultaneously in any given patient. The physician must not arbitrarily assume that a trauma patient is suffering from shock lung but should attempt to determine the specific cause. Clinical entities that should be considered in the differential diagnosis of shock lung are listed in Table 2.

Incidence

Review of trauma at San Francisco General Hospital from 1966-76 reveals 1500 trauma admissions each year. Of these, 2.8% were cases of severe respiratory failure requiring ventilatory support for 24 hours or more and fit the criteria for ARDS.

ARDS develops gradually within the first 24 hours following insult and reaches a peak in 24-72 hours. With prompt treatment of shock and pulmonary function monitoring, the early manifestation of ARDS

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*Third-year resident, Internal Medicine, Northwestern Hospital, Minneapolis, Minnesota. Presently, internist in Minneapolis.

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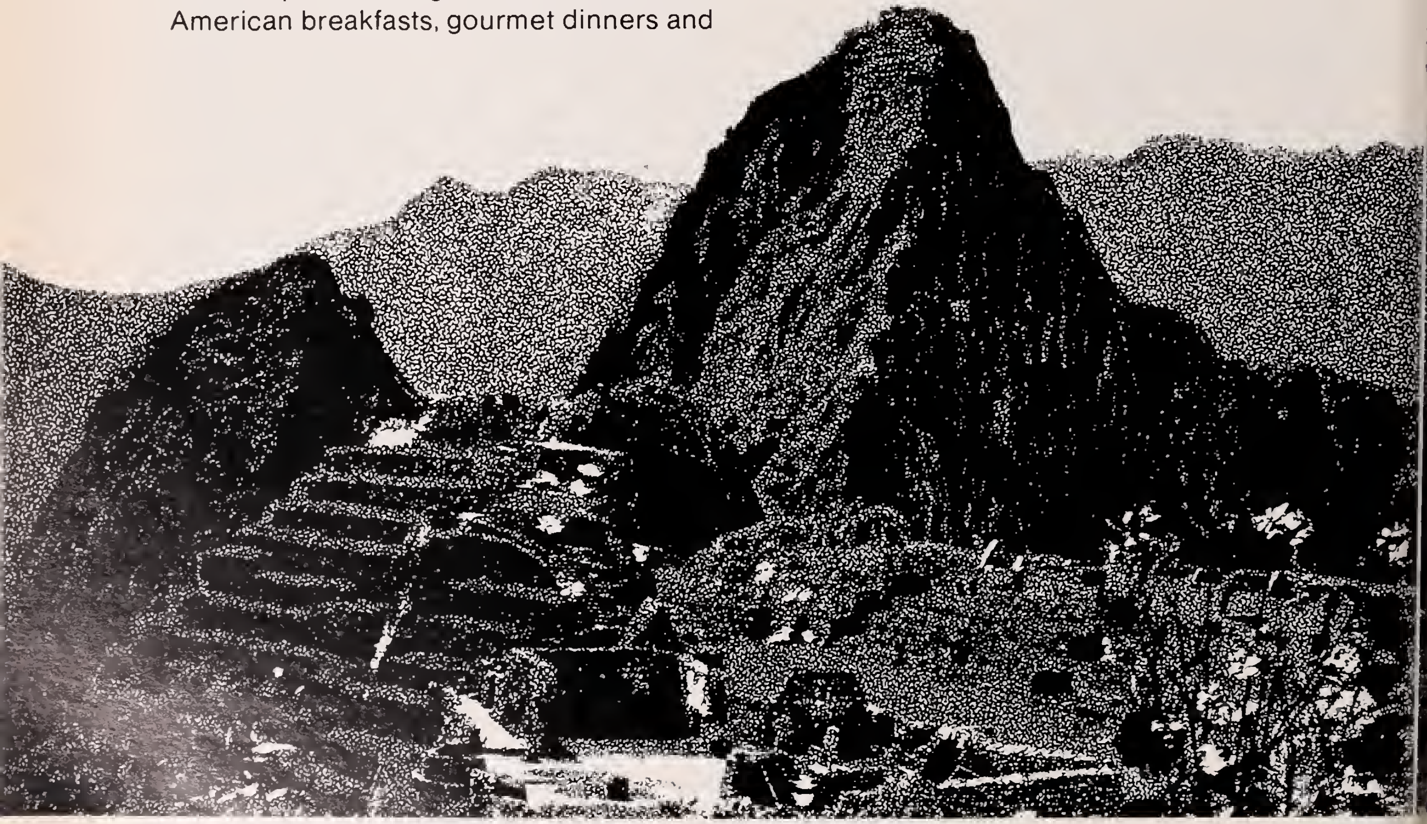

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TABLE 2

Differential Diagnosis of Respiratory Failure

Clinical Entities	Characteristics
1. Pulmonary contusion	Hemoptysis—frequent Lung changes are evident a short time after injury
2. Aspiration	Most apt to occur in the immediate post-injury period
3. Atelectasis	Commonly involves inferior and posterior portions of lung Peak incidence first 48 hours following surgery or trauma
4. Pulmonary edema	Occurs when the CVP 15-16 cm H_2O Pulmonary wedge pressure rises together with associated bubbling rales
5. Pneumothorax	Can complicate any thoracic injury
6. Pneumonia	Primarily a late complication of injury Incidence rises with degree of debility of the patient
7. Pulmonary embolus	Rarely manifest clinically prior to 7th-10th postoperative day
8. Fat embolism	Pulmonary edema without cardiac enlargement Confusion, stupor or coma, and fever and cyanosis, and petechiae

is less frequent. The peak incidence has gradually shifted to the second week after injury and is often associated with the onset of sepsis.

Clinical Manifestations

Initially, tachypnea and hyperpnea are seen. The lungs are dry to auscultation and bronchial secretions are minimal. Cardiac size and venous pressure are normal. There is decreased total compliance which requires increased pressures to ventilate. There is a progressive decrease in pO_2. pCO_2 falls secondary to hyperventilation and the increased pH reveals respiratory alkalosis. Pulmonary function tests show decreased compliance, pulmonary A-V shunting, increased respiratory dead space, and decreased functional residual capacity. The physiologic changes exceed the apparent clinical signs and symptoms.

Xray

Changes in sequential Xrays lag well behind clinical findings and changes in pulmonary function. The initial changes are a diffuse fine reticular infiltrate which corresponds to perivascular cuffing and interstitial edema. This is seen within 12 hours on the average (Figure 1A). Over the next 24 hours, this progresses to an alveolar pattern which is more diffuse and confluent corresponding to intra-alveolar edema and hemorrhage (Figure 1B). Within 24-36 hours following insult, the pattern resembles pulmonary edema. However, the heart size is normal, vascular markings are normal, the findings are more basal and lateral, sparing the apices (Figure 1C). The findings are symmetrical and bilateral. The initial patchy infiltrates may become confluent to produce dense consolidation of entire lung fields in two to three days (Figure 1D).

Etiology

The exact cause of ARDS is unknown. Nevertheless, I will consider factors mentioned most often in the literature.

1. Lung Hypoperfusion and Ischemia-Many authors have suggested that the pulmonary injury is a nonspecific vascular response to hypoperfusion caused by pneumocyte ischemia and reduced perfusion of type II alveolar cells with resultant reduced surfactant.

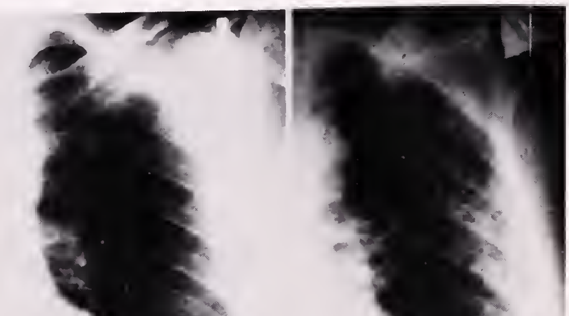

Fig. 1 (a) a diffuse fine reticular infiltrate — first (b) progresses to a diffuse confluent alveolar edema after 24 hours. (c) Pulmonary edema primarily involving basal and lateral segments with normal heart size appears within 24-36 hours. (d) Dense consolidation of the entire lung fields is seen in two to three days.

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The problem with the theory of hypoperfusion according to Blaisdell, is that lungs excluded from the circulation during shock show less damage than lungs which remain in the circulation. He cites the fact that in cardiopulmonary bypass, no effort is made to maintain lung circulation and prolonged isolation of the lungs has had no untoward effect provided that they are kept inflated while using the pump oxygenator.

2. O_2 Toxicity-The rise in cases of respiratory failure in the late 1960s raised a question as to whether the decreased respiratory function of these patients, most of whom were receiving increased increments of O_2, was due to O_2 toxicity per se. The development of O_2 toxicity is related to two factors, the O_2 dosage and the duration of exposure. In general as the concentration of O_2 rises, the duration of exposure that will cause toxicity diminishes. The exact mechanism by which O_2 produces pulmonary damage is unknown. It is most likely related to poisoning of cell enzyme systems. Breakdown in cellular function presumably results in impaired surfactant formation by Type II alveolar lining cells or decreased mucociliary function. If infused in concentrations less than 50%, it is probable that O_2 toxicity will not be a problem. Conversely when inspired concentrations of O_2 approaching 100% are necessary to maintain a normal pO_2, pulmonary damage will result after several days of administration.

3. Neurogenic Factors-It is postulated that the CNS contributes to the development of respiratory failure following shock and trauma. Lung changes following head injury are mediated through the sympathetic nervous system which produces pulmonary venoconstriction and pulmonary edema. CNS induced reflexes are probably not the cause of the ARDS but may set vicious cycles into play which may in certain instances aggravate the preexisting lung lesion.

4. Fluid Overload-Since many of the combat casualties in the Vietnam War received large quantities of fluid, the logical explanation was that fluid overload was the factor responsible for the pulmonary problems. It was thought that non-uniform perfusion of pulmonary vessels produced high perfusion pressures in certain areas of the lung leading to stretching of the pores between endothelial cells and leakage of fluid. There is no question that overenthusiastic administration of fluids will aggravate the basic underlying problem in previously damaged lungs; however, most authorities tend to deny its importance as a primary factor.

5. Sepsis-When ARDS develops within the first 48 hours following injury, it is unlikely that sepsis is the initiating event. However, with improved immediate management of trauma, a higher percentage of cases progresses to life threatening respiratory distress days to weeks post-injury. ARDS which develops at this period of time inevitably follows secondary complications usually related to sepsis. Numerous animal studies have demonstrated that the administration of endotoxin or of living bacteria causes interstitial pulmonary edema, increased pulmonary vascular resistance, decreased compliance and structural capillary damage with denuding of endothelial cells. These changes do *not* occur in perfused lungs in the absence of cellular elements of the blood. This suggests that endotoxin does not have a direct effect on lung tissue, but some other component of whole blood is necessary for the pulmonary response. The exact mechanism of pulmonary injury following sepsis is still speculative but two factors appear to be important: (1) There are gross disturbances in the clotting mechanism as well as the release of a variety of vasoactive and bronchoconstrictive substances (ie. serotonin, histamine, bradykinin, and fibrinopeptides) (2) There is direct endothelial damage to the pulmonary capillaries with resultant increase in vascular permeability. Sepsis induced intravascular coagulation has been well documented following gram negative endotoxemia in man and is capable of producing all of the pulmonary changes associated with the ARDS.

If one of the previously mentioned factors is an initiating event, the subsequent lung damage may well be the result of activation of humeral factors including serotonin, complement, histamine, kinins and the prostaglandins. Each of these agents is capable of producing bronchoconstriction, vasoconstriction, or vascular damage but none has been found in abnormal quantities in the human with respiratory failure.

6. Disseminated Intravascular Coagulation (DIC)-Tissue hypoxia, tissue injury and necrosis in shock and trauma together with associated metabolic acidosis promote intravascular coagulation. If perfusion pressure is restored to damaged tissue, the metabolic byproducts, cell debris, activated clotting factors and fibrin-platelet aggregates are flushed from the peripheral capillary beds into the pulmonary circulation. Simmons studied casualties in Vietnam and found many of the severely wounded had hematologic changes compatible with DIC. In 57 out of 120 patients followed serially after trauma there were changes in the Prothrombin Time (PT) or Partial Thromboplastin Time (PTT). The most seriously injured patients had the greatest changes. Bone found that in seven of 30 consecutive patients with the ARDS, DIC developed. These patients were characterized by having a high

incidence of bleeding, gangrene of the extremities, renal dysfunction and evidence of fibrin microthrombi in the lungs. In 12 of 23 patients who did not meet the criteria for DIC, the platelet count decreased by at least 50% during the course of their illness. Coincidental with the onset of DIC was progressive respiratory dysfunction.

Despite widespread acceptance of the pathogenic role of microthrombi in ARDS, there are still no well controlled human studies that firmly document the clinical importance of platelet or fibrin thromboemboli in the pulmonary microcirculation.

Prevention and Rx of ARDS

1. Treatment of Shock- Prompt, complete resuscitation of circulation and assurance that adequate tissue perfusion is maintained is most important.
2. Fluid Monitoring- Monitoring of intravascular volume with a Central Venous Pressure (CVP) line is essential following trauma. Also an arterial line is helpful if accurate blood pressures are difficult to obtain. However the pulmonary wedge pressure is the most accurate single number available for estimating a patient's relative volume status.
3. Respiratory Care- Preventing atelectasis is important in preventing regional hypoventilation and shunting of pulmonary blood flow. The early use of positive pressure ventilation in patients at risk for the ARDS is advised. The pulmonary shunt fraction calculation is the best single indicator of pulmonary decompensation in patients in whom shock lung develops. It parallels the pO_2 but is a better guide because it is less dependent on cardiac output.
4. Early internal fixation of fractures to permit mobility may avoid a lethal pulmonary lesion.
5. Removal of Damaged and Devitalized Tissue. High velocity bullet injuries require extensive debridement back to bleeding tissue with reoperation often within 12-24 hours to insure that all devitalized tissue has been removed.
6. Prevention of Infection-Prophylactic systemic antibiotics should be utilized prior to any surgery in heavily contaminated wounds.
7. Tracheostomy and Endotracheal Intubation-Unless injuries to mouth or upper airway are present, endotracheal intubation is preferable to tracheostomy for the early management of this syndrome. Tracheostomy is done only when the patient requires prolonged periods of ventilatory support. Criteria for intubation and ventilatory support are reviewed in Table 3.

TABLE 3

**Criteria Used to Determine
The Need for Tracheal Intubation and
Assisted Ventilation**

Respiratory Rate	> 35 per minute
Tidal Volume	< 5 ML Per Kg.
Vital Capacity	< 15 ML Per Kg.
PaO_2	< 60 mm Hg at Room Air
PaO_2 — PaO_2	> 400 mm Hg
Pulmonary Shunt	> 25%
$PaCO_2$	> 55 mm Hg

8. Ventilatory Support-Volume respirators are preferred because they are not affected by changes in compliance and deliver a constant volume to the lungs. Inspired O_2 concentrations of 40% should be the starting point for oxygenation. High tidal volumes (10-15 cc/kg) are recommended to expand the lungs. An inspired concentration of O_2 greater than 60% should be used only under extraordinary circumstances. Decreases in the pulmonary shunt fraction and increases in the pO_2 at lower O_2 concentrations can be accomplished by adding Positive End Expiratory Pressure (PEEP) at levels between five and 15 cm H_2O. The use of the membrane lung to treat advanced pulmonary insufficiency permits temporary discontinuance of the ventilator and provides a means of avoiding the high, unphysiologic ventilatory pressures which may aggravate the underlying injury.
9. Drug Treatment- Anticoagulants, steroids, colloid, diuretics, cardiac support drugs all are controversial in the treatment to varying degrees. Their optimal use has yet to be elucidated.
10. Nutritional Support of the Patient with ARDS- This may include gastrostomy feedings or total parenteral nutrition.

Outcome

Successful outcome occurs in 75-85% of patients who require intubation and mechanical ventilation. When the respiratory insult is so severe that it can not be reversed after 7-10 days of ventilation, the survival rate decreases to 50%. In spite of the potential for permanent respiratory impairment, if the patient ultimately recovers, despite prolonged respiratory failure, the prognosis is excellent.

See references page 744

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WARNINGS: If tolerance develops, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued Tenuate may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle, the patient should therefore be cautioned accordingly *Drug Dependence* Tenuate has some chemical and pharmacologic similarities to the amphetamines and other related stimulant drugs that have been extensively abused. There have been reports of subjects becoming psychologically dependent on diethylpropion The possibility of abuse should be kept in mind when evaluating the desirability of including a drug as part of a weight reduction program. Abuse of amphetamines and related drugs may be associated with varying degrees of psychologic dependence and social dysfunction which, in the case of certain drugs, may be severe. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia *Use in Pregnancy*: Although rat and human reproductive studies have not indicated adverse effects, the use of Tenuate by women who are pregnant or may become pregnant requires that the potential benefits be weighed against the potential risks *Use in Children*. Tenuate is not recommended for use in children under 12 years of age

PRECAUTIONS: Caution is to be exercised in prescribing Tenuate for patients with hypertension or with symptomatic cardiovascular disease, including arrhythmias. Tenuate should not be administered to patients with severe hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of Tenuate and the concomitant dietary regimen. Tenuate may decrease the hypotensive effect of guanethidine The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Reports suggest that Tenuate may increase convulsions in some epileptics. Therefore, epileptics receiving Tenuate should be carefully monitored. Titration of dose or discontinuance of Tenuate may be necessary.

ADVERSE REACTIONS: *Cardiovascular*: Palpitation, tachycardia, elevation of blood pressure, precordial pain, arrhythmia One published report described T-wave changes in the ECG of a healthy young male after ingestion of diethylpropion hydrochloride. *Central Nervous System*: Overstimulation, nervousness, restlessness, dizziness, jitteriness, insomnia, anxiety, euphoria, depression, dysphoria, tremor, dyskinesia, mydriasis, drowsiness, malaise, headache; rarely psychotic episodes at recommended doses. In a few epileptics an increase in convulsive episodes has been reported. *Gastrointestinal*: Dryness of the mouth, unpleasant taste, nausea, vomiting, abdominal discomfort, diarrhea, constipation, other gastrointestinal disturbances. *Allergic*: Urticaria, rash, ecchymosis, erythema, *Endocrine*: impotence, changes in libido, gynecomastia, menstrual upset. *Hematopoietic System*: Bone marrow depression, agranulocytosis, leukopenia *Miscellaneous* A variety of miscellaneous adverse reactions has been reported by physicians. These include complaints such as dyspnea, hair loss, muscle pain, dysuria, increased sweating, and polyuria

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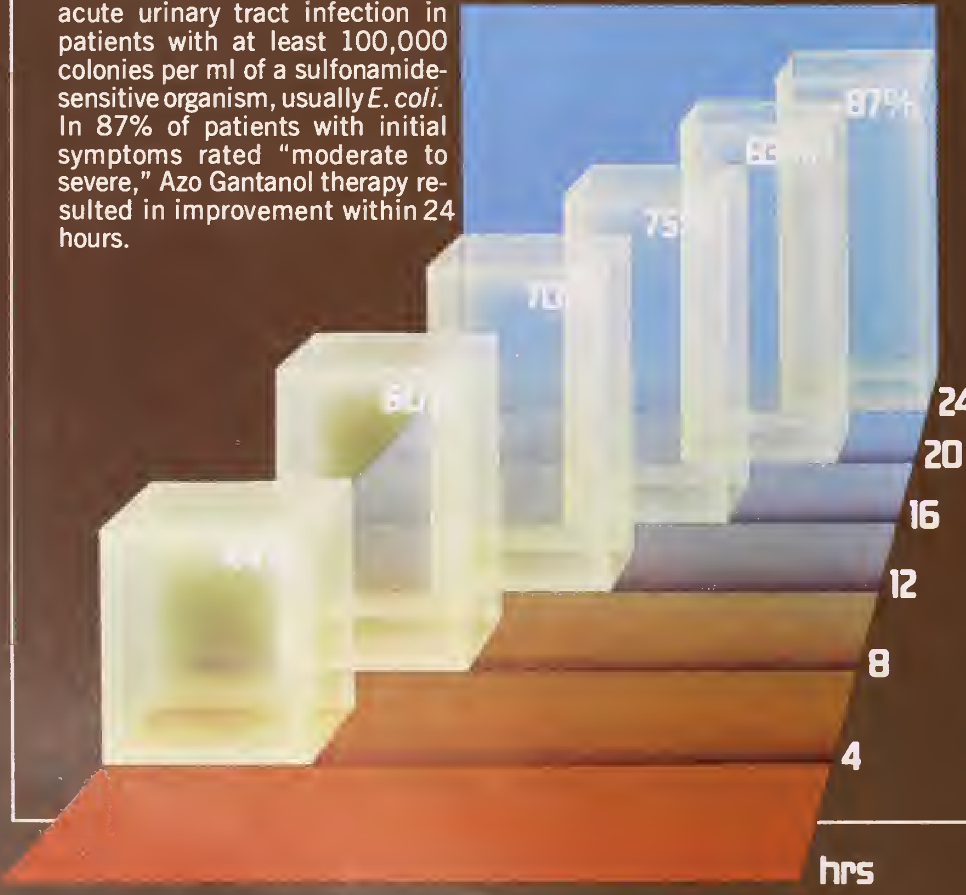

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adequate fluid intake to prevent crysta
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thrombinemia and methemoglobinemi
reactions (erythema multiforme, skin
Stevens-Johnson syndrome, epidermal
urticaria, serum sickness, pruritus, ex
dermatitis, anaphylactoid reactions,
edema, conjunctival and scleral inject
sensitization, arthralgia and allergic m
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stomatitis); *CNS reactions* (headache,
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hallucinations, tinnitus, vertigo and in
miscellaneous reactions (drug fever, c
nephrosis with oliguria and anuria, pe
nodosa and L. E. phenomenon). Due
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Obstetrics-Gynecology

Intrapartum Fetal Heart Rate Monitoring

Review of Recent Experience

EMANUEL P. GAZIANO, M.D.* and DONALD W. FREEMAN, M.D.*

One thousand and eleven intrapartum fetal heart rate records were reviewed. When the fetal heart rate was recorded as normal, outcome as measured by Apgar score at five minutes was excellent with 96.3% scoring between seven and 10. The mean Apgar score at 1 and 5 minutes was also significantly higher ($P < .001$) for the group marked "normal" when compared to the entire population. High correlations with adverse outcome were observed with certain specific heart rate patterns. The relationship between Cesarean section and various heart rate patterns is described. A brief classification of fetal heart rate patterns as related to fetal hypoxia is presented. Practical aspects of intrapartum fetal monitoring are also discussed.

ELECTRONIC FETAL HEART rate and uterine activity monitoring is now available to many obstetric services. While there is debate about the value of this type of fetal surveillance, most physicians view monitoring as potentially beneficial, particularly when related to oxytocin use or in other high-risk situations. Many of the problems relating to monitoring involve data interpretation. The clinician is asked to translate a single biophysical characteristic of the fetus (heart rate) into a decision regarding the physiologic status of the fetus and its ability to further tolerate labor. The complexity of the physiologic adjustment of the fetus in response to stress compounds the problem.

It is important to recognize that labor represents a physiologic stress to the fetus. The concepts in physiology in regard to the effect of uterine contractions on blood flow help to explain certain patterns. Uterine contractions place a repetitive stress on the fetus in the form of transient reduction of placental blood flow and oxygenation. Most term fetuses are able to tolerate this stress with minimal physiologic changes. However, a small number of fetuses will exhibit profound deterioration or even death in the presence of labor stress. It is this group that intrapartum monitoring attempts to identify.

It is hoped that the following brief review of heart rate patterns will facilitate understanding of the clinical data. The purpose of this report is to analyze recent experience in intrapartum fetal heart rate monitoring at Hennepin County Medical Center.

Fetal heart rate activity may be viewed in a practical way if one considers each of the following categories:

I. Non-hypoxic Patterns

Fetal heart rate in the range of 120 to 160 beats per

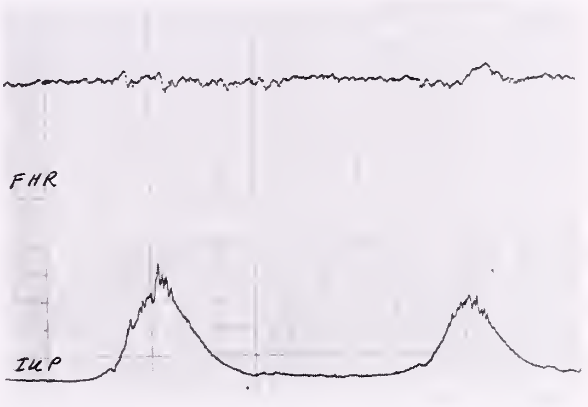

Fig. 1 — Normal FHR — note normal range with adequate beat-to-beat variability.

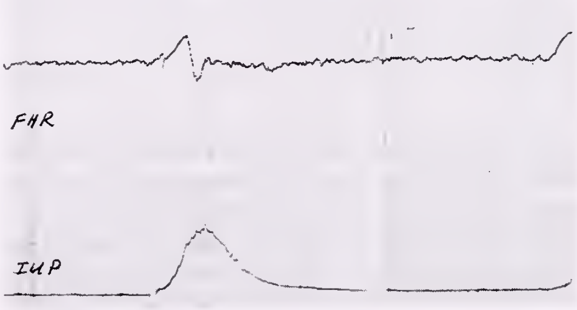

Fig. 2 — Transient acceleration of FHR indicating adequate sympathetic nervous tone.

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minute (b.p.m.) with oscillation of up to five to 15 b.p.m. is considered the normal range in the term fetus[1] (Figure 1). Transient accelerations of heart rate up to 15 to 20 b.p.m. usually indicates adequate fetal central nervous system oxygenation and represents a sympathetic response to fetal activity or movement[2,3] (Figure 2). Slowing of the rate which coincides with the uterine contraction is thought to be due to increased intracranial pressure with activation of baroreceptors and consequent activation of the vagus nerve with transient decrease in the fetal heart rate (Figure 3). All of these patterns are observed frequently during normal labor and have been correlated with good fetal outcome.

II. Patterns Induced by Hypoxia

The principal pattern under this category is late deceleration and is manifest by late slowing of the fetal heart rate following a uterine contraction (Figure 4). Late decelerations are usually indicative of fetal hypoxia. This decelerative event occurs when fetal PO_2 levels fall acutely below a critical limit[4] (probably 10 to 12 mm. of Hg. in the human). It may occur transiently due to relative maternal hypotension and decrease in intervillous space perfusion from many causes, such as maternal position, maternal blood loss or regional anesthetics. For example, maternal supine position may cause vena caval obstruction and result in decreased cardiac output and relative hypotension. This may result in a transient late slowing of the heart rate following a contraction. Frequently, treatment, such as position change, or oxygen administration can reverse this pattern under such circumstances.

Late decelerations are also observed in the chronically distressed fetus with maternal-fetal exchange of gases operating on a marginal level. Clinically, these pregnancies most often fall under one of the following diagnoses: chronic hypertension, preeclampsia, post-maturity or diabetes mellitus. Under these circumstances, the presence of late decelerations is associated with extremely high fetal and neonatal morbidity and mortality.[11]

III. Patterns which May or May not be Induced by Hypoxia

Loss of the normal beat-to-beat variability of the fetal heart rate is thought to be related to a decrease in the central nervous system stimulus to the fetal heart. In the severely asphyxiated fetus, the heart rate may be recorded as a flat line without oscillations[5] (Figure 5). In the absence of medication, this pattern is particularly ominous. However, the presence of other fetal central nervous system depressants, particularly large

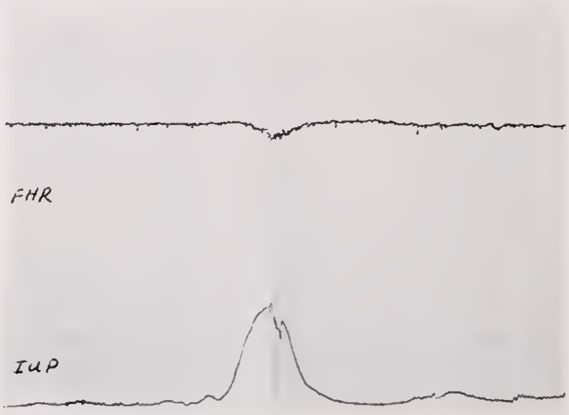

Fig. 3 — Early FHR deceleration occurring with contraction.

Fig. 4 — Repetitive late decelerations of FHR.

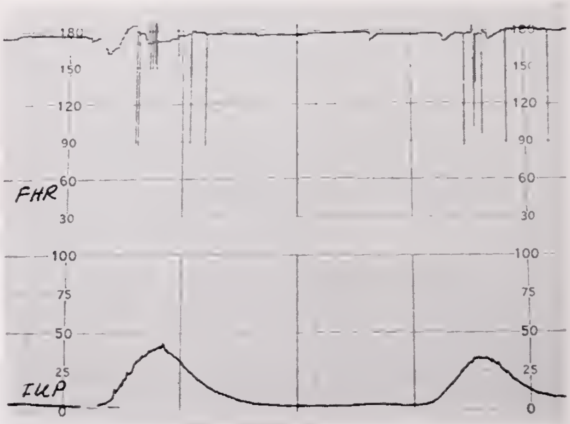

Fig. 5 — Loss of normal beat-to-beat variability and tachycardia.

doses of certain tranquilizers (Valium) or narcotics, may also produce a loss of baseline variability. Demerol, atropine, pentothal and magnesium sulfate all may cause loss of fetal heart rate variability. Fetal tachycardia (greater than 180 b.p.m.) or fetal bradycardia (less than 120 b.p.m.) may or may not be induced by hypoxia. Tachycardia may be an early response to fetal stress, but there are conflicting data as to its significance.[6] Tachycardia may be observed in the presence of maternal temperature elevation or with fetal hyperthyroidism. The significance of fetal bradycardia also may be difficult to ascertain with certainty (Figure 6). Severe prolonged fetal bradycardia of less than 100 b.p.m. results in poor outcome in a fetus with a previous normal recording, and in most fetuses, the terminal heart rate response is one of profound bradycardia. However, the significance of transient bradycardia is not always clear. Transient bradycardia may be observed following paracervical block, in the presence of maternal hypokalemia, or in the presence of fetal cardiac arrhythmia[8,9,10] Persistent bradycardia may be seen in a normally oxygenated fetus with certain cardiac abnormalities.

IV. Reflex Parasympathetic Activity which, if severe, may result in Fetal Hypoxia

Transient umbilical cord occlusion results in a rapid deceleration which is usually V- or U-shaped in configuration and is thought to be mediated by reflex vagal activity (Figure 7). If prolonged or severe, umbilical cord occlusion may result in decreased fetal cardiac output and a decrease in the fetus' ability to maintain homeostasis and oxygenation. This pattern may be classified as to degree of severity in terms of duration of heart rate decelerations and degree of drop in the heart rate. A severe cord compression pattern, for example, would be a 60 b.p.m. fall or greater with a duration of 60 seconds or more. Cord compression if severe, recurrent and repetitive may be associated with fetal asphyxia.

V. Mixed Patterns

It is not uncommon to observe mixed heart rate patterns during intrapartum monitoring. Certain combinations of patterns are associated with fetal asphyxia. For example, fixed baseline with loss of variability and tachycardia, and the changing from one pattern to another were observed in more than 50% of stressed infants in one large series.[11] Others have noted increased morbidity in the presence of cord compression patterns associated with baseline changes, such as tachycardia or bradycardia.[12]

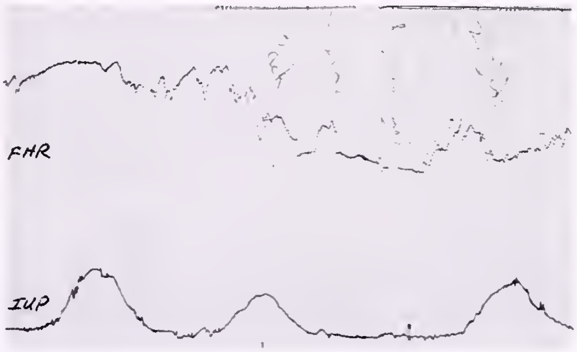

Fig. 6 — Transient fetal bradycardia.

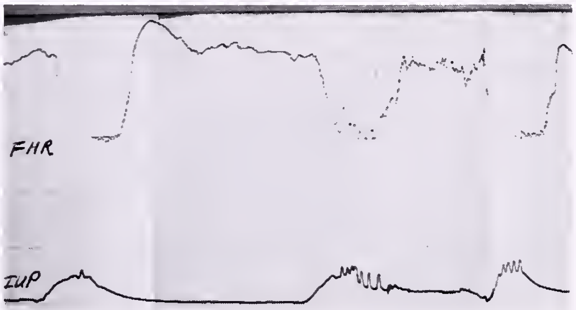

Fig. 7 — Variable deceleration pattern, severe.

Materials and Methods

One thousand and eleven consecutive intrapartum fetal heart rate monitor records were reviewed. A fetal monitor history is maintained on each monitored patient. These data include age, parity, gestational age, indications for monitoring, and type of instrumentation used. Further breakdown of indications relate to complications of fetal, maternal or uterine origins. After completion of monitoring, records were reviewed and fetal heart rate observations, as well as mode of delivery, birth weight and Apgar scores were recorded. A total of 64 variables was available for analysis. The fetal heart rate observations were recorded, and the history sheets were then reviewed for accuracy and completeness. The data were tabulated and a computer analysis was made with cross tabulation of certain variables.

Results

Table 1 indicates outcome as manifested by Apgar score* when certain heart rate patterns were observed.

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*A measure of the newborn's physiologic status with a score assigned from 0 to 10, 7-10 considered vigorous, 4-6 moderately depressed, 0-3 severely depressed.

These data do not reflect exclusive groupings of fetal heart rate patterns. As noted, when the fetal heart rate pattern was normal, 96.3% scored Apgars of between seven and 10 at five minutes of life. With the presence of any other fetal heart rate pattern in the record, the predictive value for high Apgar at five minutes falls to 89.3%. This is significantly different from those marked normal at the $P < .002$ level. The mean Apgar score at one minute for a normal fetal heart rate was 7.75, compared to 7.32 for the entire population ($P < .001$). At five minutes, the mean Apgar score for the normal group was also higher at 8.84, as compared to 8.53 for the entire population, also statistically significant at the $P < .001$ level. Table 2 reflects the

TABLE 1

Outcome as Related to FHR Patterns

	Apgar Score at 5 Minutes		
	0-3	4-6	7-10
FHR normal	9* (2.2%)	6 (1.5%)	390 (96.3%)
FHR any other pattern	25 (4.1%)	42 (6.9%)	543 (89.0%)

*Number and percentage of patients falling under each category.

TABLE 2

Outcome as Related to Specific FHR Patterns

	Apgar Score at 5 Minutes		
	0-3	4-6	7-10
FHR Normal	9* (2.2%)	6 (1.5%)	390 (96.3%)
Early Decelerations	0 (0.0%)	11 (5.8%)	179 (94.2%)
Variable Decelerations	10 (2.7%)	24 (6.3%)	343 (91.0%)
Late Decelerations	3 (3.3%)	12 (13.0%)	77 (83.7%)
Tachycardia	3 (3.0%)	7 (7.0%)	90 (90.0%)
Bradycardia	5 (4.1%)	8 (6.6%)	109 (89.3%)
FHR Loss of Variability	3 (3.1%)	11 (11.5%)	82 (85.4%)

*Number and percentage of patients falling under each category.

TABLE 3

Mean Apgar at 5 Minutes of Life as a Function of Presence or Absence of Specific FHR Pattern

	Present	Not Present	Significance
Early Deceleration	8.72	8.48	.07
Variable Deceleration	8.49	8.55	.59 (NS)
Late Deceleration (UPI)	8.15	8.57	.02
Tachycardia	8.45	8.53	.61 (NS)
Bradycardia	8.27	8.56	.07
Loss of Variability	8.21	8.56	.06

TABLE 4

Late Decelerations and Apgar Score

	Apgar Score at 5 Minutes		
	0-3	4-6	7-10
Late deceleration present (%)	3.3	13.0	83.7
Late deceleration absent (%)	3.4	3.9	92.7

TABLE 5

Mode of Delivery as Related to Specific FHR Patterns

	Vaginal		C-Section	
	(N)	(%)	(N)	(%)
FHR — Normal	361	(89.8)	41	(10.2)
Early Decelerations	183	(96.3)	7	(03.7)
Variable Decelerations	359	(95.2)	18	(04.8)
Late Decelerations	65	(70.7)	27	(29.3)
Tachycardia	80	(80.0)	20	(20.0)
Bradycardia	103	(84.4)	19	(15.6)
Loss of Variability	78	(81.7)	18	(18.3)

percentage of newborns with Apgar scores at five minutes, as a function of certain heart rate patterns. When late decelerations or loss of fetal heart rate variability were present in the record, 16.3% and 14.6% respectively, of the neonates were either moderately or severely depressed at birth. The mean Apgar score at five minutes for specific patterns is presented in Table 3. At five minutes, those with late decelerations, loss of variability, or bradycardia present in the record scored significantly lower Apgar scores than when these patterns are not present. Patients with early decelerations had higher Apgar scores, while no differences were noted for tachycardia or cord compression pattern. Table 4 indicates distribution of Apgar scores when late decelerations are present in the record. Sixteen and three-tenths percent were either moderately or severely depressed at five minutes. Twenty and six-tenths percent of the patients scored 0 to 3 on the Apgar scale at one minute of life when late decelerations were present. In the absence of late decelerations, only 7.2% of the patients scored in this low range.

The overall Cesarean section rate of the monitored group was 10.0%. This compares to a hospital rate for this time period of 7.3%. Table 5 indicates the relationship between mode of delivery and fetal heart rate patterns. Ten and two-tenths percent Cesarean section rate was recorded when the fetal heart rate was marked normal. The overall Cesarean section rate with the presence of cord compression was 4.8%, which was actually lower than the entire population. The presence of late deceleration or loss of fetal heart rate variability in the record increased the Cesarean section rate for 29.3% and 18.3% respectively, indicating appropriateness of Cesarean section based on heart rate observations. Twenty percent of patients with baseline tachycardia underwent Cesarean section. Although tachycardia was not associated with poor outcome, it may be that this pattern was associated with other poor prognostic patterns, such as loss of variability.

Discussion

The present findings tend to support the observations of others that in the presence of a normal fetal heart rate record, the probability of good outcome is extremely high.[13,14] However, it might be noted that 3.7% of the patients with a normal fetal heart rate record were depressed at birth (Apgar or six of less). Although specific analysis was not made, some of these probably represented traumatic deliveries or neonatal depression from drugs or anesthesia. The other patterns observed in our series are in general agreement with the view that late decelerations and loss of fetal heart rate variability are associated with untoward fetal outcome. Bradycardia in our series was associated with less than optimal outcome. Tachycardia and cord compression patterns alone did not appear to result in poor outcome as measured by five minute Apgar score. However, the duration and severity of these patterns were not considered in this analysis. The Cesarean section rate in this group of patients was not appreciably increased because of intrapartum fetal monitoring. Frequent criticism of monitoring is that it may increase the Cesarean section rates without decreasing perinatal mortality statistics. In fact, the overall Cesarean section rate for cord compression pattern was decreased in this group. The performance of Cesarean section for fetal distress appeared to be related to poor prognostic patterns. From these data, we are not able to infer a specific relationship between abnormal fetal heart rate patterns and Cesarean section. Certainly ominous patterns occurring early in labor and not correctable by usual means were principal factors in the decision to perform Cesarean section. In addition, an abnormal tracing in the presence of other labor complications, such as dystocia, may have influenced the performance of Cesarean section.

As a clinical tool, fetal monitoring lends an added dimension to intrapartum care. As in other clinical situations, the progress of labor, the patient's medical condition, the stage of labor and duration of gestation are considered in decisions regarding patient management.

If the fetal heart rate is normal, it is extremely reassuring. In the presence of an ominous pattern, such as repetitive late decelerations, or severe variable deceleration, and loss of baseline variability occurring early in labor, termination by Cesarean section may be warranted. In the presence of an abnormal pattern, treatment in the form of maternal position change, discontinuing oxytocin use, and oxygen administration should be employed. However, in the presence of mixed or equivocal patterns, further diagnostic aides may be necessary in the form of fetal scalp blood sampling. Many obstetric units at present do not have the ready availability of this technique or individuals who are experienced in evaluating such data. Continuous pH or PO_2 monitoring of the fetus may obviate some of the difficulty in record interpretation in the future.

From a practical view, internal fetal monitoring with an intrauterine catheter and a scalp electrode is invaluable in the adjustment and safe administration of oxytocin in high-risk pregnancy situations. It affords the least possible oxytocin dosage in the most efficient conduct of the labor. The use of monitoring in the diagnosis and treatment of uterine dysfunction is of great value in those situations in which there is failure of progression. Intrapartum monitoring allows the clinician to begin to think in terms of the fetus as a unique patient, measuring just one of its vital signs. In the future, it may be possible to measure other parameters of the fetal physiologic state in an attempt to eliminate intrapartum asphyxia.

Acknowledgment

We are grateful for the assistance of David L. Hill, M.D., whose careful reading and recording of the fetal heart rate tracings made this study possible. We also wish to thank Tom Allen and the University of Minnesota Computer Center for their statistical assistance.

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Rheumatology Corner

Extra-Articular Manifestations of Rheumatoid Arthritis

H. S. LUTHRA, M.D.*

RHEUMATOID ARTHRITIS is a chronic, disabling disease of unknown etiology in which joint involvement dominates the clinical picture but, in some patients, extra-articular manifestations may stand out and require that treatment be directed against them.

Hematologic Manifestations

Anemia is the commonest manifestation. This is similar to the anemia of chronic disease characterized by normocytic, normochromic erythrocytes associated with a low serum iron and decreased or normal saturation of iron-binding protein. In addition, the use of a variety of drugs may lead to a superimposed iron deficiency anemia. Estimation of iron stores by bone marrow examination is the only reliable technique to determine whether or not true iron deficiency exists in these circumstances. Administration of iron is indicated only when the bone marrow iron stores are decreased or absent.

Leukopenia may develop in rheumatoid arthritis. The constellation of leukopenia with or without splenomegaly often associated with skin ulcers and recurrent bacterial infections is termed Felty's syndrome. Although treatment with some drugs such as lithium or testosterone may be associated with an increase in the white blood cell count, there is very little evidence that these forms of treatments actually benefit the patient. Treatment, instead, should be directed against the underlying disease with the use of such agents as gold or penicillamine. Since these drugs are capable of producing bone marrow suppression, this form of therapy should be administered under very strict control. Splenectomy will usually be followed by an increase in the white blood cell count but this improvement is usually shortlived and, splenectomy should be reserved only for patients with serious or life-threatening infections or incapacitating leg ulcers.

Cardiac Manifestations

Pericarditis is found at autopsy in 10-50 percent of the patients with rheumatoid arthritis but is almost always benign during life and most often asymptomatic. If pericarditis becomes a significant problem and other causes of pericarditis have been excluded, then treatment should be directed towards the suppression of the underlying disease with use of gold, penicillamine or even corticosteroids. Pericardiectomy is rarely, if ever, indicated.

Rheumatoid nodules can occur on the valves and give rise to valvular dysfunction. Myocardial involvement by rheumatoid nodules rarely leads to heart block and even more rarely congestive heart failure.

Rheumatoid Nodules

Rheumatoid nodules are most commonly seen in the subcutaneous areas of the body, especially those exposed to mechanical pressure. These can vary in size from a few millimeters to several centimeters in diameter and are usually asymptomatic. The nodules rarely can ulcerate, become infected or threaten to cause tendon rupture. If this occurs, surgical treatment is indicated. Rheumatoid nodules in other organs, such as the lung or the bone, can cause great diagnostic difficulty but rarely are symptomatic.

Eye Involvement

Keratoconjunctivitis sicca is extremely common in rheumatoid arthritis. In addition, episcleritis occurs fairly commonly. This is rarely symptomatic and the majority of the patients require no treatment. Use of local corticosteroid eyedrops helps the few symptomatic patients.

Scleritis, however, represents a more serious form of eye involvement. This can proceed to scleromalacia perforans and may require immediate and aggressive treatment. This complication often requires local and systemic corticosteroids.

Vasculitis

Although histological evidence of vasculitis is commonly demonstrable in rheumatoid arthritis, significant clinical lesions leading to ischemia with infarction of the skin, digits, peripheral nerves and bowel are far less common. Manifestations of vasculitis include livedo reticularis and skin infarcts. Periungual infarcts in and off themselves are of little importance.

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If significant vasculitis with symptomatic involvement of a digit, viscus, or nerve occurs, high dose corticosteroid treatment is essential.

Neuropathy

Entrapment neuropathies commonly occur in rheumatoid arthritis and are really a manifestation of the synovitis of anatomically related tenosynovium. Local injections of corticosteroids may provide relief, but surgical treatment should not be withheld if symptoms are not completely relieved so that irreversible muscular atrophy can be avoided.

Peripheral sensory neuropathy due to direct involvement of sensory nerves is not uncommon but fortunately is not significant. More significant neuropathy is heralded by the sudden onset of severe pain and paresthesias followed by loss of motor function in the distribution of the affected nerve. When more than one nerve is involved, the process is termed mononeuritis multiplex and is due to necrotizing vasculitis of the vasa nervorum. This complication has significant prognostic importance since the mortality rate of 40-70 percent has been associated among such patients. Treatment with high dose oral and parenteral corticosteroids should be begun immediately in such patients followed by institution of a plan of therapy which permits suppression of the overall disease activity and reduction of their corticosteroid dose.

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For use in the treatment of infant colic (syrup)

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS: Obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); obstructive disease of the gastrointestinal tract (as in achalasia, pyloroduodenal stenosis); paralytic ileus, intestinal atony of the elderly or debilitated patient, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis. WARNINGS: In the presence of a high environmental temperature, heat prostration can occur with drug use (fever and heat stroke due to decreased sweating). Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy In this instance treatment with this drug would be inappropriate and possibly harmful. Bentyl may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery or perform hazardous work while taking this drug. PRECAUTIONS: Although studies have failed to demonstrate adverse effects of dicyclomine hydrochloride in glaucoma or in patients with prostatic hypertrophy, it should be prescribed with caution in patients known to have or suspected of having glaucoma or prostatic hypertrophy. Use with caution in patients with: Autonomic neuropathy Hepatic or renal disease. Ulcerative colitis. Large doses may suppress intestinal motility to the point of producing a paralytic ileus and the use of this drug may precipitate or aggravate the serious complication of toxic megacolon. Hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, and hypertension Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition.

Do not rely on the use of the drug in the presence of complication of biliary tract disease Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate With overdosage, a curare-like action may occur ADVERSE REACTIONS: Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these Adverse reactions may include xerostomia; urinary hesitancy and retention, blurred vision and tachycardia; palpitations; mydriasis; cycloplegia, increased ocular tension, loss of taste, headache, nervousness, drowsiness; weakness; dizziness; insomnia, nausea, vomiting; impotence, suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION Dosage must be adjusted to individual patient's needs.

Usual Dosage Bentyl 10 mg capsule and syrup: *Adults* 1 or 2 capsules or teaspoonfuls syrup three or four times daily *Children* 1 capsule or teaspoonful syrup three or four times daily. *Infants* ½ teaspoonful syrup three or four times daily (May be diluted with equal volume of water.) Bentyl 20 mg *Adults*. 1 tablet three or four times daily Bentyl Injection: *Adults*: 2 ml. (20 mg) every four to six hours intramuscularly only NOT FOR INTRAVENOUS USE. MANAGEMENT OF OVERDOSE. The signs and symptoms of overdose are headache, nausea, vomiting, blurred vision, dilated pupils, hot, dry skin, dizziness, dryness of the mouth, difficulty in swallowing, CNS stimulation. Treatment should consist of gastric lavage, emetics, and activated charcoal. Barbiturates may be used either orally or intramuscularly for sedation but they should not be used if Bentyl with Phenobarbital has been ingested. If indicated, parenteral cholinergic agents such as Urecholine® (bethanecol chloride USP) should be used.

Product Information as of October, 1978.

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Special Article

Prevalence of Intestinal Parasites in a Laotian Immigrant Community

NEAL R. HOLTAN, M.D.,* KENT B. CROSSLEY, M.D.,* and CONSTANCE N. PRIES, M.D.*

From May 1976 to June 1978, 157 recent Laotian immigrants received health care at a federally-funded community clinic. Review of these patients' clinic records indicated that 56 (35%) had had stool examinations for ova and parasites; 38 of the 56 (70%) yielded one or more intestinal parasite. Because of the apparent high prevalence of parasites in this population, a survey was conducted of all 195 Laotian immigrants living within the designated boundaries of the community clinic. Three stool specimens were obtained from each subject. The overall prevalence of intestinal parasites was 54 of 195 subjects (27.7%); 25 persons with *Giardia lamblia* (12.8%) and 24 with hookworm (12.3%) accounted for the majority of positive specimens. None of 20 children born of Laotian immigrant parents in the United States was infected. A large majority of subjects with giardial infestation (20/25) and with hookworm (22/23) perhaps would not have been identified if only a single stool specimen had been examined. A high prevalence of parasitic infestation occurred with hookworm in the 10-19 year age group (23.1%) and with *Giardia* (31.4%) in the 2-5 year age group. Gastrointestinal symptoms occurred in one of the 54 subjects with positive stool examinations and in three of the 136 subjects with negative examinations.

BETWEEN 1976 AND OCTOBER, 1978, there were approximately 140,000 Southeast Asian refugees who immigrated to the United States. Ten thousand of these came from the country of Laos[1]. Half of about 400 Laotians who have come to St. Paul, Minnesota, received their medical care at one community clinic. Because refugees from Vietnam in the United States were found to have a high prevalence of helminthic infestation[2], the studies reported here were undertaken.

Population and Methods

The Laotians in St. Paul lived in rural, mountainous areas before coming to the United States in the spring of 1976. Settling in public housing complexes in the economically depressed Summit-University area, they tend to live in extended family units of fairly large size with persons of all ages. This paper reports findings from a retrospective review of clinic records and the results of a prospective study for parasites in this population.

Chart Review

The medical charts of the 157 Laotian patients who had visited the clinic between May 1976 and June 1978 were reviewed by the medical staff for results of stool examinations. Patients with a positive stool examination for ova and parasites were identified and the results of the examinations tabulated. Stool examinations were performed by the Minnesota Department of Health. The purpose of the chart review was to determine the need for a community-wide survey. Because of ongoing relocation, persons in this review were not necessarily part of the population present within the defined boundaries of the clinic when the survey was initiated in June 1978.

Population Survey

The leaders of the cohesive Laotian community perceived parasitic infestation as a major health problem and provided a list of the 195 persons of Laotian origin within the defined service boundaries of the clinic. A public health nurse and an interpreter visited each of the 31 households to verify the list, to leave the first specimen container for each member of the household, and to instruct the subjects in collection. A second, and then a third container was distributed when the subjects returned the specimens to the clinic's field office. The specimens were preserved in 10% formalin, processed using the formalin-ether method of Ritchie[3], and analyzed by experienced

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*Model Cities Health Clinic and the Department of Medicine, St. Paul-Ramsey Medical Center, St. Paul, Minnesota; and the Department of Internal Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.

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parasitology technicians working in the clinic's laboratory.

Treatment and Education

The clinic's nurse practitioner conducted the treatment program under a protocol designed by the clinic's physician. A community outreach worker carried out an educational program designed for the population. Goals of the education were to warn against *Diphyllobothrium latum* in raw Minnesota fish and to teach good handwashing and food sanitation.

Results

Chart Review

Of 157 Laotian persons who had visited the clinic between 1976 and mid-1978, 56 patients for various reasons had had a stool examination for ova and parasites. Of these 56, 38 (70%) had evidence of at least one intestinal parasite and had received treatment (Table 1). One patient, a 61-year-old woman, had amebic dysentery.

Population Survey

Of the 195 persons in 31 households, 99 were under the age of 17. About 20% of persons over 16 were employed. There were 36 persons who had received prior treatment for intestinal parasites, 29 of whom were included in the chart review mentioned above. Of the total number in the survey, four persons (2%) complained of gastrointestinal symptoms on interview, of whom only one was found to have parasites (hookworm and *Giardia).* Table 2 displays the distribution of parasites identified in the survey. There were 54 of 195 (27.7%) individuals with positive stool examinations. This group of 195 people included the 29 with past treatment documented at the clinic, and excluding them brings the fraction positive to 51/166 (30.3%). Combining those persons with positive stool examinations in the survey and those negative in the survey but with positive stool examinations in the past, 73 of 195 (37.4%) had past or present parasitic infestation.

Other Observations

One person who had clinical dysentery and *Entamoeba histolytica* on stool examination again had positive specimens on examination during the survey three months after treatment. Eight of ten persons treated in the past for *Giardia* had negative stool

TABLE 1
Results of Chart Review*

Organism	Age					Total
	2-5	6-9	10-19	20-39	40	
Ascaris	3	1	1	1	—	6
Hookworm	1	2	10	5	4	22
Clonorchis sinensis	—	—	3	—	—	3
Taenia solium	—	—	1	—	—	1
Giardia lamblia	3	2	4	3	3	15
Entamoeba histolytica	—	—	—	—	1	1

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*Of the 56 patients with stool examination for ova and parasites, 38 were positive. Multiple infections occurred with *Giardia* and hookworm (two persons), Ascaris and hookworm (three persons), hookworm and *Clonorchis* (one person), and hookworm and *Taenia* (one person).

TABLE 2
Organisms Found In Three Sample Stool Surveys of 195 Persons.*

Organism	Age						Total
	0-1	2-5	6-9	10-19	20-39	40	
Giardia lamblia	0/20	11/35	7/20	2/39	4/55	1/22	25/195
Entamoeba histolytica	0/20	0/35	0/20	1/39	1/55	1/22	3/195
Hookworm	0/20	3/35	3/20	9/39	6/55	3/22	24/195
Trichuris	0/20	1/35	1/20	5/39	0/55	0/22	7/195
Enterobius vermicularis	0/20	1/35	0/20	0/39	0/55	0/22	1/195

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*All three specimens were negative in 135 persons; six persons (five from the 10-19 year age group) did not comply with collections. Multiple infections included: *Giardia* and hookworm (three persons), *Trichuris* and hookworm (two persons), *Giardia* and *Enterobius* (one person), and *Entamoeba histolytica* and hookworm (one person).

examinations in the survey, with a mean of 15.3 months between treatment and the survey. All of 15 persons treated for hookworm in the past had negative examinations in the survey, and for *Ascaris*, all of five.

When a pathogen was present in at least one of the three specimens, the number of times that it appeared in two or all three was low (Table 3). A large majority of subjects with giardial infestation (20/25) and with hookworm (22/23) perhaps would not have been identified if only a single stool specimen had been examined.

TABLE 3
Number of Positive Specimens Given That One Was Positive.

Organism	1 of 3	2 of 3	3 of 3
Giardia	14	6	5
Hookworm	20	2	1
E. histolytica	2	1	0
Trichuris	6	1	0

Viewing the results by family unit, no patterns were noted. With *Giardia*, positive examinations occurred in persons who were scattered among half of the households. No family had a majority of members infected with *Giardia*. The three persons who were found to have *E. histolytica* lived in separate households.

The prevalence of parasitic infestation varied substantially with age. None of the 20 children (those under age two) born in the United States had positive stool examinations for parasites. Hookworm was found in nine of 39 subjects ages 10-19 (23.1%) in the survey. *Giardia* was most common in the two to five year age group with 11 of 35 persons (31.4%) having positive examinations.

Discussion

The prevalence of parasitic infestation in persons living in rural Southeast Asia is high. A survey among rural Malaysian school children of Chinese, Indian, and Malay origin showed the helminthic infection rates to be 60%, 87%, and 95%, respectively[4]. For similar children in urban schools, the rates were lower (22%, 48%, and 50%). A survey among persons of all ages in three Indonesian villages showed that *Ascaris* and *Trichuris* were common in all age groups, while the prevalence of hookworm infection increased with age[5]. Parasitic infection in that survey occurred with equal frequency in the two sexes. Both surveys employed one stool specimen per subject.

In Laos, a survey using single stool specimens collected from 2,493 persons in Vientiane and its environs in 1973 revealed *E. histolytica* in 1.1%, *Giardia* in 8.3%, *Ascaris* in 49.3%, hookworm in 30.6%, and *Trichuris* in 9.0% of subjects[6]. Students in three different schools were given three specimen containers, one for himself and the other two for any other members of his family, so the results do not represent random sampling of the population. Direct comparison with the results from the study reported here is not possible.

As found in this Laotian immigrant population in St. Paul, other immigrant groups have yielded high prevalence rates of parasitic infection. A survey of Latin-origin school children, predominantly Puerto Rican, in Hartford, Connecticut, demonstrated 54% of the children to have intestinal parasites[7]. The survey was hampered by a low compliance rate (62%) and by the use of a single stool specimen. About one-third of the subjects had *Trichuris* and one-quarter *Giardia*. Hookworm (5%) and *E. histolytica* (2%) were uncommonly found. Length of residence in the continental United States could not be correlated with the prevalence of parasites, but nativity was an important determinant.

Some Laotian refugees may have been included in a survey for intestinal parasites conducted in the American Vietnamese refugee centers in 1975[2]. Over 1,000 individuals were screened using single stool specimens. *Ascaris* (30.5%), *Trichuris* (9.0%) and *Giardia* (8.2%) were commonly found; *E. histolytica* (2%) and hookworm (4.1%) were less frequent. Explanations for the apparent differences between those results and the findings of the survey reported here are not readily evident.

Multiple specimens are perhaps more useful than a single stool specimen in detecting parasites. The number of specimens required to do so is not known and may depend on the organism in question or the method of preservation of the samples. Toddlers in day care centers in Georgia were investigated during an epidemic of diarrhea[8]. Of 37 stool specimens positive for *Giardia*, 32 (86%) occurred on the first specimen of the three obtained. Only 3% were found for the first time on the third specimen. In another study[9], 22 of 30 patients found to have *Giardia* on a duodenal aspirate had cysts in the stool on the first specimen. The remainder showed cysts in the second specimen. These studies conflict with the results of the study reported here in that *Giardia* was found in 14 of 25 (56%) infected persons in only one of the three samples analyzed.

Because the formalin-ether method of preserving specimens can underestimate the prevalence of either cystic or cellular protozoans as opposed to helminth eggs[10], the present study may have found an even higher incidence of protozoa if other methods of stool preservation, such as poly-vinyl alcohol (PVA) had been feasible. The survey performed in the Georgia day care centers[8] revealed that PVA preservation of stool specimens resulted in finding one of the 37 cases that had not been identified by the formalin-ether preservation.

It appears that parasitic infestation among immigrants does not abate quickly and spontaneously. In a survey done in Chicago among Puerto Rican-born persons, the prevalence of hookworm infestation did not decline significantly until after two or three years' residence in the continental United States[11]. The study among Latin-origin school children[7] showed that prevalence of parasitic infection after one year of residence in the continental United States was 88%, while after three to five years, the rate had decreased to 78%.

Acknowledgments

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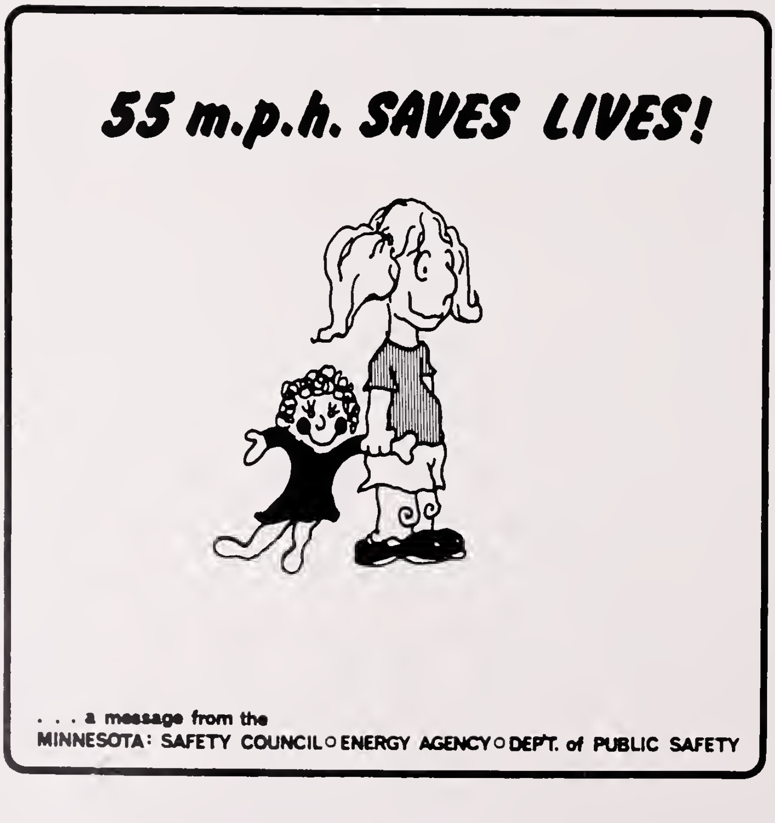
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Minnesota Department of Health

Suggestions for Medical Screening of Southeast Asian Refugees

ANDREW G. DEAN, M.D., M.P.H.*

Over 3,000 refugees from Southeast Asia may arrive in Minnesota during the next year, according to some estimates, and over 4,000 are already residing in the state. The Center for Disease Control is responsible for medical screening of refugees while they are still abroad, including examination for tuberculosis, leprosy, venereal disease and mental defects and disorders. Reports from a variety of federal sources indicate, however, that the quality of screening varies and that general medical examination on arrival in a U.S. community will insure treatment of general medical problems, provide for immunization and generally pave the way for future medical care. Although the U.S. Public Health Service is making an effort to improve the screening received in Asia, this is complicated by the fact that refugees are screened at a large number of different sites in Asia.

The overseas screening may improve in the future; meanwhile, the following suggestions are provided for physicians caring for newly arrived Southeast Asian refugees. These comments are intended to supplement the general medical examination for clinically apparent problems such as malnutrition or anemia which are commonly found in this group.

Tuberculosis

This is perhaps the only condition presenting a significant risk to members of the general public in contact with refugees. Twenty-six cases were found among Southeast Asians in Minnesota in 1978. We suggest the following screening procedure if the patient has not previously been screened by a facility of known reliability: (1) Persons through age 21 should be skin tested using needle, syringe and PPD. (2) Persons over 21 should receive both a skin test and a chest Xray.

A skin test reaction of 10mm. or more of induration, regardless of BCG status, should be considered a true positive for purposes of prophylactic treatment. Positive skin test reactors through age 21 should receive a chest Xray, and other evaluation as needed, to rule out active disease. Persons though age 21 infected without disease should receive one year of preventive therapy. (This is true up to age 35 if reliable monitoring for side effects of isoniazid can be arranged.) All persons with active disease should receive at least 12-18 months of therapy, with at least two drugs, chosen with the aid of drug susceptibility tests. Smear positive cases should be treated with three drugs.

Immunization

Physicians should not assume that this has been accomplished. Active steps, including follow-up, should be taken to insure that children have received a full series for measles, rubella, mumps, pertussis (under age six), diphtheria, tetanus and polio. Adults should receive tetanus and diphtheria toxoids.

Intestinal Parasites

Most are detected by stool examination. Although multiple stool examinations will detect more infections, treatment is not advised for many helminths unless egg counts are high, and those with high counts should be positive with a single specimen. *Ascaris* should be treated if present at all, and hookworm and *Trichuris* should be treated if large numbers of eggs are present. Mebendazole (Vermox) may be used to treat all three (plus pinworms) if the patient is not pregnant. Giardia may be treated with one of three drugs: quinacrine hydrochloride (Atabrine), metronidazole (Flagyl) or fluorazolidone (Fluroxone), but all three have disadvantages. A recent article suggests quinacrine hydrochloride for giardia in adults, and fluorazolidone for children.[1] Other parasites, including *Clonorchis sinensis,* should not be treated unless symptoms are present. Consultation on recommended treatment for other parasites is available through the Acute Disease Epidemiology Unit at 612/296-5414.

Malaria and Venereal Disease

There have been very few clinical cases of malaria, syphilis or gonorrhea reported in Minnesota's SE

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*State Epidemiologist, Minnesota Department of Health, Minneapolis, Minnesota.

Asian population. Screening for these conditions is of secondary importance unless clinically suspected.

Leprosy

This has been uncommon so far. We are aware of only one case residing in Minnesota. The disease is detected by inspection of the skin. Macular depigmented lesions, particularly if anesthetic to pinprick, or nodules along the course of major peripheral nerves should suggest further work up.

Inspection for lice and scabies is suggested, although these conditions may also be uncommon.

Services for interpreters may be obtained through Catholic, Lutheran and International Institute social service organizations in various parts of the state. Information relating to social service or public welfare may be obtained from Jane Kretzmann, Minnesota Department of Public Welfare (phone 296-8140).

The Hennepin County Chest Clinic (phone 348-3031), the St. Paul Model Cities Health Clinic (224-4601), and the St. Paul Health Department (227-7741) provide screening services for residents of their areas.

In addition to standard medical or tropical medicine textbooks, or texts such as *Current Therapy*, recommendations and dosages for treatment of parasitic conditions are contained in the *Handbook of Antimicrobial Therapy* published by *The Medical Letter* (1978).

Advice on treatment of tuberculosis can be obtained from Dr. H. Richard Johnson, tuberculosis consultant to the Minnesota Department of Health (612) 348-3031. Tuberculosis is a reportable disease and should be reported without delay to the local public health agency and/or to the Minnesota Department of Health (612) 296-5414.

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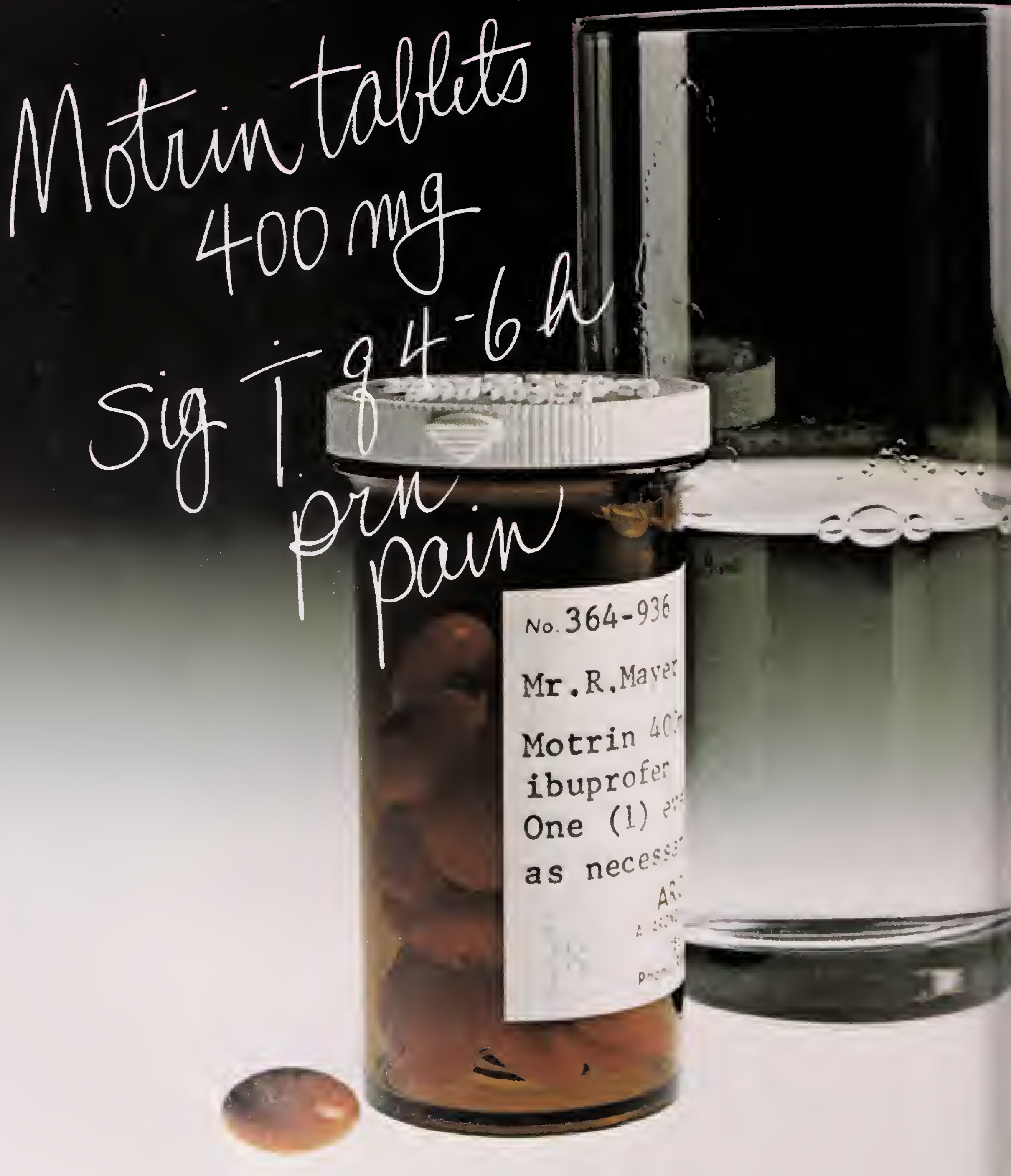
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Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

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Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

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Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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Minnesota Medical Association

Cataract Surgery

THE COMMITTEE ON OPHTHALMOLOGY of The Minnesota Medical Association feels that it is their duty and obligation to put in perspective some of the methods that are now being employed in cataract surgery. Recently, there has been considerable publicity about phacoemulsification and intraocular lens insertion in the communication media. The enthusiasm of these reports often portrays the "new" methods so superior to the conventional methods, so as to almost render the older methods obsolete in the minds of the reader. These new surgical procedures have some merit, but neither phacoemulsification nor intraocular lens insertion has been proven to be the best procedure in all cataract surgery, in fact the scientific data that is now being compiled indicates that there are definite contraindications to these new methods in certain cases. The Committee On Ophthalmology joins with other ophthalmologists in condeming the way these relatively new surgical procedures have at times been exploited.

Basically there are two kinds of cataract surgery: one in which the lens is first broken and removed in pieces from the eye (extracapsular); the second, in which the lens is removed from the eye in one piece without fragmentation (intracapsular). When cataract surgery was first performed, the lenses were usually removed by fragmentation, because at this time there was no good method of removing them in one piece. Recent innovations have greatly improved the surgeon's ability to remove cataracts in one piece and doing cataract surgery in this way is successful in over 95% of the cases, one of the most successfùl operations in medicine. In the past ten years, some surgeons have adopted the fragmentation method, employing the phacoemulsification or suction technique. When used in properly selected cases by a well trained surgeon with properly functioning equipment, fragmentation can also yield good results. Either method is approved; however, one method may be preferable in a specific case. The choice of method will be a matter of judgment for the ophthalmologist. There are some complications, which are more likely in phacoemulsification than in the standard intracapsular cataract technique. Among these we find iris trauma, opacification of the lens capsule (after cataract membrane) and corneal clouding. The long term effect of some of these complications has not yet been determined and probably will not be evaluated for at least another decade.

Whichever technique is used for removing the cataract, the eye must have some type of optical correction for it to see clearly after the operation. There are three ways by which this can be accomplished: One is by placing a pair of cataract spectacles in front of the eye. The second is by wearing a contact lens, and the third is by having an intraocular lens placed inside the eye. Intraocular lenses are plastic implants which are inserted into the eye at the time of surgery. Because the intraocular lens implant can provide optic correction without the magnification of the spectacle lens and the nuisance of contact lens manipulation, ophthalmologists have tried for thirty years to find a satisfactory intraocular lens. During the past five or so years, several types of intraocular lenses have become available and are being used and investigated by some eye surgeons. When considering intraocular lenses, the patient should be made aware of the fact that implantation of an intraocular lens increases the risk of cataract surgery. Some complications which can occur in any type of cataract surgery are much more serious, when one has implanted an intraocular lens, such as a flat chamber and hemorrhage. There are also complications which are unique to intraocular lens insertion. These include damage to the cornea during insertion, dislocation of the lens, increased incidence of intraocular inflammation, the "dazzle" reflex and operative procedures needed to adjust or remove an offending lens. Studies have shown that there may be some significant damage to the back of the cornea with use of the intraocular lens as evidenced by decrease in corneal endothelial cells. There is no long term data yet available to currently assess the affect of the damage over an extended period of time. The ideal intraocular lens is still being sought. Drews and other investigators have shown by electron microscopy that there is a need for better fabrication and quality control of intraocular lenses. Because of the accumulating reports of complications from implants, The Food and Drug Administration in 1977 set new regulations that limit all intraocular lenses to investigational use only.

The Committee On Ophthalmology of The Minnesota Medical Association strongly urges anyone desiring an intraocular lens implant or phacoemulsification to talk the decision over very carefully with their ophthalmologist. If there are any questions one should obtain a second consultation from an ophthalmologist not associated with the ophthalmologist recommending the surgery.

The presence of a cataract is not an automatic indication for cataract surgery. The amount of functional disability that is caused by the cataract determines the need for surgery. This would vary depending upon the person's need.

Phacoemulsification and lens implants are just two additional procedures in the ophthalmologist's surgical armamentarium; their utilization requires good ophthalmic judgment to determine which procedure is best in a specific case. (Beware of the ophthalmic surgeon who claims that his method and skill in one form of cataract surgery are the best).

This statement is issued to offset the notion that a "newer" procedure is necessarily better than more conventional procedures.

Committee on Ophthalmology
Minnesota Medical Association

ALTHOUGH THE UNITED WAY IS IN THE BUSINESS OF GIVING AWAY MONEY, WE DON'T JUST GIVE IT AWAY.

United Way

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Classified advertising rates are forty (40) cents a word; minimum monthly charge $10.00, key number, $1.50 additional Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 101 East 5th, Suite 900, St. Paul, Minn. 55101.

FAMILY PRACTICE opportunities in outstanding Southern Minnesota Group. The Albert Lea Clinic, P. A., is interested in contacting physician candidates for city and small town branch practices. This group is a 16 man multispecialty group in the primary and secondary care fields. Top salary first year. Senior physician participation beginning at the end of the first year, in incentive income distribution plan. Low cost buy in. Maximum profit sharing plan. Top level insurance plan and full range of other benefits. New hospital in city. Albert Lea is an exceptional place to live and these are choice practices. Please contact B. J. Boss, Administrator, Albert Lea Clinic, P. A., 1602 Fountain St., Albert Lea, MN 56007, Phone 507-373 8251, personal phone 507-377 1406 or contact Gary Boeke, M.D., 507-373 8251, personal phone 507-826-3288.

TWO INTERNISTS — Wanted to join an 11 physician multi-specialty group. Hospital equipped for colonoscopy and gastroscopy. Located in a progressive city of 13,000 with excellent schools and recreational area around a chain of 5 lakes. If interested, call or write: Don Grandgenett, Administrator; Fairmont Medical Clinic P.A., 800 Clinic Circle, Fairmont, MN (507) 238-4263.

FAMILY PRACTITIONER wanted. 25 doctor multi-specialty group in scenic Hiawatha Valley needs Family Practitioner to staff a branch office 18 miles from the main clinic. Doctor may opt to live in Winona or the rural community. Diversified recreation. Excellent public and parochial school systems, including three four-year colleges. The Clinic currently is successfully staffing one branch office, and is committed to staff a second. Must be Board certified or Board eligible. Salary guaranteed. Liberal fringe benefits, including pension plan and profit sharing plan. Incentive system after one year. For additional information, write or call Dr. Andrew E. Edin, Chairman, Recruiting Committee, Winona Clinic, Ltd., 420 E. Sarnia Street, Winona, MN 55987. (507) 454-3680.

THE FARIBAULT CLINIC, LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

PRACTICE WHERE there is an abundance of clean air and outdoor activities — in the heart of Minnesota's lakes and woods. Excellent opportunity for 1 F.P. to join with 6 F.P's., 2 General Surgeons and 2 Physician Assistants. New clinic building. 50 bed hospital with 5 bed ICU-CCU. Contact William Pauley, Park Rapids-Walker Clinics, LTD., 120 N. Main, Park Rapids, MN 56470. Phone 218/732-3325.

OPHTHALMOLOGIST WANTED IN SOUTHERN MINNESOTA Group Practice. The Albert Lea Clinic, P.A., in Albert Lea, Minnesota, a 16 man multi-specialty group is seeking a replacement for a senior man. Board certified or Board eligible. Salary guaranteed first year. Second year, participant in clinic's incentive income distribution plan. Low cost buy-in arrangement. Profit sharing plan. Top insurance plan with full range of other benefits. New hospital in city. A choice practice and exceptional place to live. Contact William Brouwer, Assistant Administrator, Albert Lea Clinic, P.A., 1602 Fountain Street, Albert Lea, Minnesota 56007, phone 507-373-8251, personal phone 507-889-6381 or contact Gary A. Boeke, M.D., 507-373-8251, personal phone 507-826-3288.

WANTED: GP to join two GP's in practice in rural community northern Minn. Mod. clinic bldg. with good xray & lab facilities. 40 bed hosp; 100 bed nursing home. Also need locum tenans for summer vacations. Contact W. A. Pinsonneault, MD, Warren Clinic, box 107, Warren, MN 56762 (218) 745-4151.

APPLICATIONS WELCOMED from board-qualified or certified radiologists. Large teaching hospital, upper midwest; University affiliation. Subspecialty training in nuclear medicine desirable. Box 529, Minnesota Medicine, 101 E. 5th St., St. Paul 55101.

(Continued to page 764)

The Maker

Examining a Few Myths About Prescribing.

Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand–name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of th generics. Drug nomenclature is not the important point; it's the compe tence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

(Continued from page 761)

FAMILY PRACTITIONER, OB-GYN, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

FAMILY PHYSICIAN to join expanding group of family physicians. Downtown Minneapolis location adjacent to Metropolitan Medical Center. Contact Donald Blowers, M.D., or Roxanne Butler, Business Manager, Parkside Family Physicians, P.A., 825 South 8th St., Mpls., Mn. 55404. Phone 375-1700.

FIFTY PHYSICIAN multi-specialty clinic in western Wisconsin wants Family Practitioner to work in nearby satellite offices. Excellent cultural, educational and recreational facilities. 90 miles from Minneapolis. Please contact G. E. Owen, M.D., Midelfort Clinic, Ltd., 733 W. Clairemont Avenue, Eau Claire, WI 54701 or call 839-5222.

GENERAL SURGEON or internist needed to take over 27 year practice by May-July, 1980, in two college city. 42 miles from Twin Cities. Write: MINNESOTA MEDICINE — 543 — 101 E. 5th St. #900, St. Paul 55101.

FAMILY PHYSICIAN wanted to join active practice with two family physicians and general surgeon. Generous starting salary with a full range of benefits. Located one hour southwest from Twin Cities. Growing community with excellent recreational and educational opportunities. New clinic with community hospital nearby. Contact: Jo E. Anderson, M.D. or Duane R. Schultz, Business Manager, Minnesota Valley Medical Associates, 301 Valleygreen Square, Le Sueur, Minnesota 56058. Phone (612) 665-3391.

WANTED— M.D. or D.O./FAMILY PRACTICE to join gr. of 3 FP/MD's. Exc. new clinic attached to 120 bed hosp. Full hosp. priv. avail. Salary 1st yr. then may join corp. Thriving comm. of 10,000 + with lg. drawing area. Fine recreational and social area with first class school system & all churches avail. Easy freeway access to metro area. Contact Family Clinic, 808 3rd St. S.E., Little Falls, MN 56345 or call collect D. R. Seifert M.D. (days) 1-612-632-2301, (evenings) 1-612-632-9150.

ORTHOPAEDIC SURGEON, Internist and OB-GYN for multi-specialty group with a Family Practice Department, Crookston, Minnesota. New clinic facility, full partner in one year. Located in the heart of the Red River Valley with stable economy. Call R. R. Schnabel, M.D. collect at 218-281-3184, Crookston, Minnesota.

OBSTETRICIAN-GYNECOLOGIST, to join 11 member primary care group. 7 Family Physicians, 2 Internists and 2 General Surgeons. Large patient population, newly remodeled and expanded Clinic facility approximately 6 blocks from modern, well equipped 99 bed hospital. Rural community 45 minutes South of the Metro area on 35W. Salary guarantee first year. For more information please contact: Darral Mischke, Clinic Administrator, Faribault Clinic, Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

ORTHOPEDIC SURGEON, Ophthalmologist, and Pediatrician wanted. A 25 doctor multi-specialty group in scenic Hiawatha Valley is searching for an Ophthalmologist, a second Orthopedic Surgeon, and a third Pediatrician. Diversified recreation, excellent public and parochial school systems including three four-year colleges. Person must be Board certified or Board eligible. Salary guaranteed plus good potential earnings. Liberal fringe benefits including pension plan and profit sharing plan. Drawing area of 60,000. For additional information, write or call Dr. Andrew E. Edin, Chairman, Recruiting Committee, Winona Clinic, Ltd., 420 E. Sarnia Street, Winona, MN 55987. (507) 454-3680.

WANTED: Family Practice physician to join group of four. Clinic situation ½ mile from modern 280 bed hospital. Extensive privileges available to qualified Family Practitioner. Clinic handles a wide variety of patient problems including surgery and obstetrics. Excellent area for potential growth for medical practice. For more information, contact John C. Bordwell, M.D., or East Main Clinic, 850 E. Main Street, Anoka, MN 55303, phone (612) 421-7070.

FAMILY PHYSICIAN SEEKING POSITION Young, Residency trained, Board Certified Family Practitioner, with practice experience in Minnesota, desires part time position in or near Minneapolis-Saint Paul area. Practice and/or administrative opportunities considered. Write: Minnesota Medicine — 545, Suite 900 101 E. 5th St., St. Paul 55101.

EXCELLENT OPPORTUNITY for two or three family practitioners in small, stable economic community serving 15,000 population. Move into a new clinic attached to 38 bed, well equipped JCAH accredited hospital. One physician now working in the four man clinic. No investment is necessary and you'll be guaranteed a liberal salary with many fringes. Enjoy the many advantages of small community living while living in an area that offers diversified recreational activities, excellent schools and a warm environment. Write or call Omer Eischens, Hospital Administrator, Tracy Municipal Hospital, Tracy, Mn. 56175. Phone collect: 507-629-3200.

OUTSTANDING OPPORTUNITY for two family physicians and one surgeon to join young group of six, Board certified family physicians, one general surgeon who is a fellow of the American College of Surgery, one physician's assistant and one Ph.D. family counselor. The new 11,000 square foot clinic is located just Southwest of the Minneapolis metropolitan area and offers excellent access to the downtown area while offering the advantages of small-town living. The Shakopee area also possesses an outstanding school system. In the Summer of 1980, it is anticipated that an 8,000 square foot expansion will be completed by the clinic and will be located in Prior Lake, Minnesota. Both the clinics will be serviced by St. Francis Hospital (126 bed, full-service facility). The Shakopee Medical Center offers early buy-in possibilities and excellent fringe benefits. For further information contact Donald Lynch, M.D. or David C. Fleming, Clinic Administrator at the Shakopee Medical Center, 1335 East Tenth Avenue, Shakopee, MN, 55379 or phone 612-445-1305.

ANESTHESIOLOGIST needed in outstate Minnesota. Should be board certified or eligible. Department has 300+ cases per month. Malpractice insurance paid. $60,000 first year, then buy in. Write: Minnesota Medicine — 547, Suite 900, 101 E. 5th St., St. Paul 55101.

OPENINGS FOR family physicians, internists and psychiatrists in Minnesota's 9 state hospitals. Salary $40,000-$60,000. Regular hours, liberal benefits. Call Ronald C. Young, M.D., Dept. of Public Welfare (612/296-3058).

FAMILY PRACTITIONERS needed immediately to join present four physician corporate group practice in rural Southwestern Minnesota; guaranteed income with liberal fringe benefits; full partnership after one year; no investment necessary; new clinic facility attached to newly renovated hospital; area offers excellent recreational activities; top school systems; warm community atmosphere. Contact J. L. Bader, M.D., Chief of Staff, Slayton Clinic, 2042 Juniper Avenue, Slayton, MN 56172; Phone number: (507) 836-6153 or 836-6463.

OB-GYN SPECIALISTS DESIRED. Enjoy the security of group practice with the freedom of independent practice. If you are Board Certified or Board Eligible in OB-GYN, we have an interesting opportunity for you. One or two specialists are needed immediately to form an independent OB-GYN practice in a very desirable Northern Wisconsin community with a drawing population of 65,000. Active practice assured. All major specialists available for consultation. Business advice, technical and legal, will be provided. Outstanding personal benefit programs available. Income potential great. Generous starting income guaranteed. A 35 million dollar hospital just opened with available office space. For further information call (715) 842-3202, or write Mr. Lloyd Engstrom, P.O. Box 1646, Wausau, Wisconsin 54401.

G.P. OR F.P. needed to continue practice from which I wish to retire. 100 Bed Hospital. Excellent consultants. Best little city of 17,000 in State. D. J. Studer, M.D., Faribault, MN. 55021. Tel: 507-334-5960.

FAMILY PRACTICE SUBURBAN MINNEAPOLIS Private practice opportunity with established group near modern accredited hospital. Must be Board Eligible or Board Certified and do OB. No weekend call. Excellent referral centers and continuing medical education in adjacent city. Family oriented suburban location. Reply with curriculum vitae in confidence to MINNESOTA MEDICINE (549), 101 East 5th St., #900 St. Paul, Minnesota, 55101.

(Continued on page 766)

(Continued from page 565)

WANTED: GENERAL PRACTITIONER to join well established medical group. Complete clinic facilities and full hospital privileges. Liberal educational and vacation time. Guaranteed salary and opportunity for early partnership. Rose-Jensen-Manabat, 621 E. Walnut Street, Green Bay, Wis. 54301. Telephone 414-437-4366.

FAMILY PRACTICE RESIDENTS: If you wish to practice family medicine the way you have been trained and be the physician of your full potential, Swift County Family Physicians is your style. Contact K. P. Olson, M.D., or J. V. Springrose, M.D., at Swift County Family Physicians, 1805 Wisconsin Ave., Benson, Mn. 56215. 612-843-4944.

FOR SALE OR Lease Brick bldg. over 3000 sq. ft. suitable medical office space, 683 Dodd Rd., St. Paul. Priced at $89,500.00. Twins Realty, Inc. 698-1900 or 482-8973.

FAMILY PHYSICIAN, internist or surgeon willing to do family practice to join three board certified family physicians in growing small community with expanding industry. New hospital well equipped, excellent consultation services. New clinic being built attached to hospital. Please contact Mrs. Annabel C. Greseth, Administrator, Johnson Memorial Hospital, Dawson, MN 56232, phone 612-769-4323; or contact P. W. Maus, M.D., Chief of Staff, Box 249, Dawson, MN 56232, phone 612-769-4393.

FAMILY PHYSICIAN to join two Board-Certified family doctors, one physicians assistant, and one family counselor in a young and growing medical practice in beautiful Central Minnesota. The practice is oriented towards holistic medicine with a commitment to patient and community education. 80 minutes to downtown Minneapolis. Cultural and recreational activities in abundance. Salary range $35-43,000 depending on qualifications. Contact Adm. Douglas F. Adamek or Thomas J. Newton, M.D. at Cold Spring Medical Clinic, 26 N. Red River Ave., Cold Spring, MN 56320 — 612-685-8641.

WANTED: 1, 2, or 3 PHYSICIANS for partially equipped Doctors Building in Buffalo, Minnesota, 30 miles west of Minneapolis. Contact Herbert Winge, M.D., 1311 Viking Drive, Buffalo, MN 55313. Or telephone 1-612-682-4881 on weekends.

FULL-TIME POSITION available for Family Physician in the Department of Family Practice, St. Paul-Ramsey Medical Center. Over the past 7 years solid relationships have been developed with the other specialties within this institution and the residency has become well established. Thus I believe your environment would be pleasant and challenging. We prefer applicants with board certification, social concerns, and a desire to teach residents and care for patients. We would also encourage physicians who might like to spend 1 or 2 years with us and then return to their current practice. This could be a nice change of pace and you would have considerable impact at a critical time in the Family Practice movement. For further information, please address inquiries and curriculum vitae to Vincent R. Hunt, M.D., Director, Department of Family Practice, St. Paul-Ramsey Medical Center, St. Paul, Minnesota 55101, 612-221-3540.

FAMILY PRACTICE RESIDENTS: Swift County Family Physicians is seeking dynamic residency-trained FP with ideas, to join us in the rewards of practicing innovative high-quality family medicine in West Central Minnesota. Contact K. P. Olson, M.D., or J. V. Springrose, M.D., 1805 Wisconsin Ave., Benson, Mn. 56215, 612-843-4944.

FAMILY PRACTITIONER to join 14 man primary care group, seven Family Practitioners, two Internists, two Surgeons, OB-GYN, Pediatrician and Urologist. Modern Clinic, 1½ blocks from three year old 100 bed hospital. Salary first year, extensive fringe benefits. Contact Thomas A. Treanor, M.D., Albert Lea Medical and Surgical Center, Albert Lea, MN 56007.

PRACTICE OPPORTUNITIES AVAILABLE — in Family Practice and various specialties in the Midwest. We specialize in matching the interests and needs of the individual physician with available practice situations. We offer confidentiality and professional representation as we help you locate the particular position you seek. The opportunities listed with us vary in both practice and community size. All fees are paid by the employer. Please direct inquiries to: MEDICAL CAREERS, 633 Medical Arts Building, Minneapolis, Minn. 55402 (612/339-6640) — Perry C. Harrison, Physician Recruiter.

INTERNIST — 29, University trained, ABIM eligible, seeks partnership or group practice in Twin Cities area. Contact David Walcher, 3901 Woodmont Ave., Toledo, Ohio 43613.

efore prescribing, please consult complete product information, a ummary of which follows:

he effectiveness of Valium (diazepam) in long-term use, that is, more than
months, has not been assessed by systematic clinical studies. The
hysician should periodically reassess the usefulness of the drug for the
dividual patient.

ontraindications: Tablets in children under 6 months of age; known
/persensitivity; acute narrow angle glaucoma; may be used in patients
ith open angle glaucoma who are receiving appropriate therapy.

arnings: As with most CNS-acting drugs, caution against hazardous oc-
upations requiring complete mental alertness (*e.g.*, operating machinery,
iving). Withdrawal symptoms (similar to those with barbiturates, alcohol)
ave occurred following abrupt discontinuance (convulsions, tremor,
odominal/muscle cramps, vomiting, sweating). Keep addiction-prone indi-
duals (drug addicts or alcoholics) under careful surveillance because of
edisposition to habituation/dependence.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

AL: Advise patients against simultaneous ingestion of alcohol and other
IS depressants.

t of value in treatment of psychotic patients; should not be employed in
of appropriate treatment. When using oral form adjunctively in convul-
e disorders, possibility of increase in frequency and/or severity of grand
l seizures may require increase in dosage of standard anticonvulsant
edication; abrupt withdrawal in such cases may be associated with tem-
rary increase in frequency and/or severity of seizures.

ECTABLE: *To reduce the possibility of venous thrombosis, phlebitis, local*
ation, swelling, and, rarely, vascular impairment when used I.V.: inject
wly, taking at least one minute for each 5 mg (1 ml) given, do not use
all veins, i.e., dorsum of hand or wrist, use extreme care to avoid intra-
erial administration or extravasation. Do not mix or dilute Valium with
er solutions or drugs in syringe or infusion flask. If it is not feasible to
minister Valium directly I.V., it may be injected slowly through the infusion
ing as close as possible to the vein insertion.

minister with extreme care to elderly, very ill, those with limited pulmo-
y reserve because of possibility of apnea and/or cardiac arrest, con-
nitant use of barbiturates, alcohol or other CNS depressants increases
oression with increased risk of apnea, have resuscitative facilities avail-
e. When used with narcotic analgesic eliminate or reduce narcotic dos-
at least 1/3, administer in small increments. Should not be administered
oatients in shock, coma, acute alcoholic intoxication with depression of
l signs.

s precipitated tonic status epilepticus in patients treated for petit mal
us or petit mal variant status.

hdrawal symptoms (similar to those with barbiturates, alcohol) have oc-
red following abrupt discontinuance (convulsions, tremor, abdominal/
scle cramps, vomiting, sweating). Keep addiction-prone individuals
ler careful surveillance because of predisposition to habituation/
endence. Not recommended for OB use.

acy/safety not established in neonates (age 30 days or less); pro-
ged CNS depression observed. In children, give slowly (up to 0.25
kg over 3 minutes) to avoid apnea or prolonged somnolence; can be
eated after 15 to 30 minutes. If no relief after third administration,
ropriate adjunctive therapy is recommended.

cautions: If combined with other psychotropics or anticonvulsants,
efully consider individual pharmacologic effects—particularly with known
ipounds which may potentiate action of Valium (diazepam), *i.e.*,
nothiazines, narcotics, barbiturates, MAO inhibitors and antidepres-
s. Protective measures indicated in highly anxious patients with ac-
panying depression who may have suicidal tendencies. Observe usual
autions in impaired hepatic function, avoid accumulation in patients
compromised kidney function. Limit oral dosage to smallest effective
unt in elderly and debilitated to preclude ataxia or oversedation (ini-
2 to 2½ mg once or twice daily, increasing gradually as needed or
ated).

INJECTABLE: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

Adverse Reactions: Side effects most commonly reported were drowsiness, fatigue, ataxia. Infrequently encountered were confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, discontinue drug.

Because of isolated reports of neutropenia and jaundice, periodic blood counts, liver function tests advisable during long-term therapy. Minor changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during and after Valium (diazepam) therapy and are of no known significance.

INJECTABLE: Venous thrombosis/phlebitis at injection site, hypoactivity, syncope, bradycardia, cardiovascular collapse, nystagmus, urticaria, hiccups, neutropenia.

In peroral endoscopic procedures, coughing, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat or chest have been reported.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Use levarterenol or metaraminol for hypotension, caffeine and sodium benzoate for CNS-depressive effects. Dialysis is of limited value.

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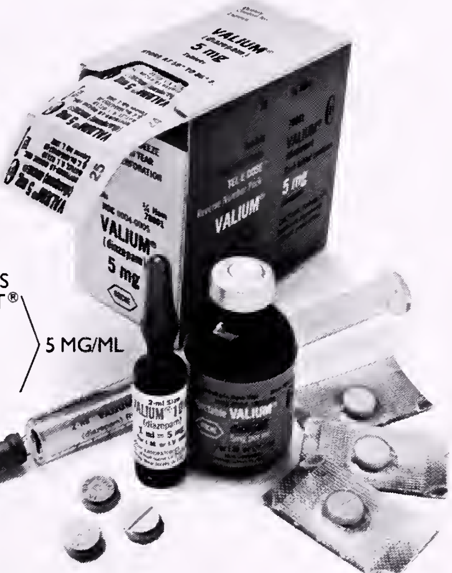

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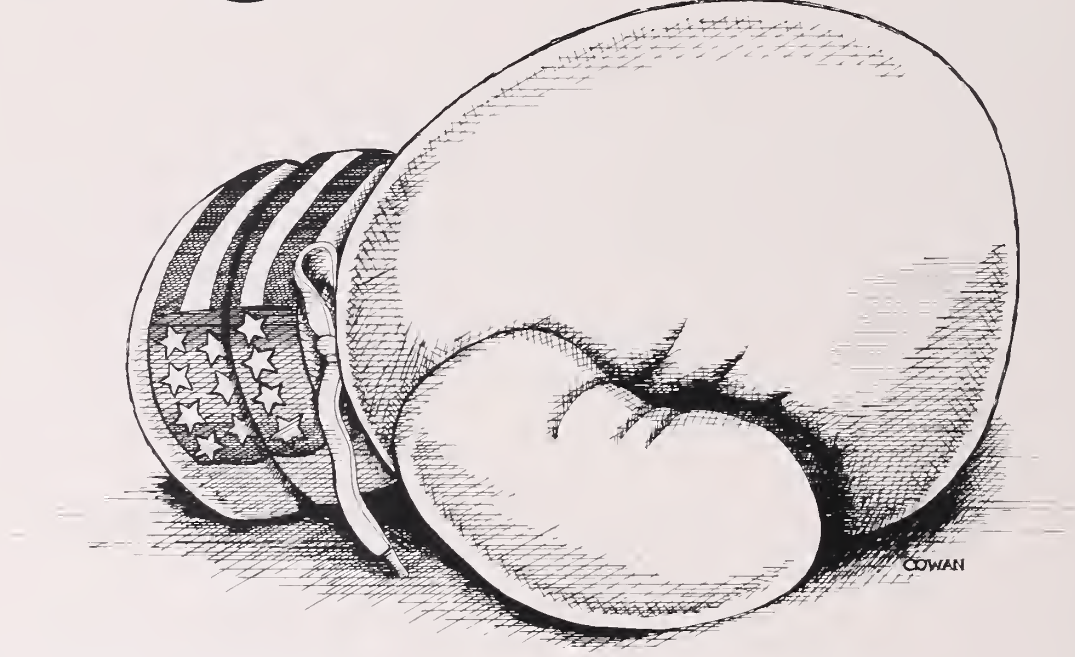

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	50,000	15,400	4,400	19,800	30,200

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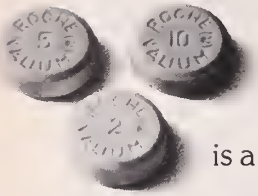
A character all its own.



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Another important aspect of the clinical character of Valium is safety. Though drowsiness, ataxia and fatigue are possible, these and more serious side effects are rarely a problem. Of course, as with all CNS-acting drugs, patients taking Valium should be cautioned against driving, operating dangerous machinery or the simultaneous ingestion of alcohol.

Unquestionably, many psychotherapeutic agents, including other benzodiazepines, have antianxiety effects. But one fact remains: you get a certain kind of patient response with Valium. It's a response you want. A response you know. A response you trust as part of your overall management of anxiety and psychic tension.

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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

The effectiveness of Valium (diazepam/Roche) in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

> ***Usage in Pregnancy:*** **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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Contents — November, 1979

COVER PHOTOGRAPH — "Superior North Shore"
Earl Henrikson, M.D. ... 780

PRESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association ... 771

ORIGINAL CONTRIBUTIONS

Appendicovesical Fistula
Culley C. Carson, III, M.D. and Reza S. Malek, M.D. ... 773

Necrotizing Fasciitis — A Lethal Infection
Richard F. Kyle, M.D. and Ramon B. Gustilo, M.D. ... 775

Liver Injury Secondary to Radiation Therapy for Breast Cancer
Neil R. Hoffman, M.D. ... 778

Proximal Tibial Metaphyseal Fractures in Children — A Complication
Richard J. Aadalen, M.D. ... 785

Septicemia and Pleural Effusion from Eikenella Corrodens A Normal Mouth Inhabitant (Corrected Version)
Paul Stiegler, M.D. ... 789

Congenital Factor VII Deficiency — Safety of Surgery without Preoperative Transfusion
R. D. Niedringhaus, M.D. et al. ... 791

EDITORIALS

HMOs — Their Limitations and Role
Alfred F. Anderegg, M.D. ... 797

LEGAL — **Legal and Ethical Aspects of Pre-Employment Physical Examinations**
Richard C. Cohan, M.D. ... 799

LABORATORY LETTER — **Infant at Risk for Early Onset Group B Streptococcal Infection**
Ralph A Franciosi, M.D. ... 801

INDO-CHINESE REFUGEES — **Detection and Chemo Prophylaxis of Tuberculosis in Southeast Asian Immigrants**
R. B. Breitenbucher, M.D. ... 805

SPECIAL ARTICLE — **Survival after Coronary Artery Bypass Surgery-Significance of Preoperative Left-Ventricular Function**
Charles R. Peterson, M.D. and H. K. Helseth, M.D. ... 813

MINNEAPOLIS HEALTH DEPARTMENT — **Low Birth Weight Births to Girls Enrolled in the Minneapolis Pregnant School Girl Program**
Ellen Alkon, M.D. and Gertrude Carlson, B.A. ... 822

RURAL PHYSICIAN ASSOCIATE PROGRAM — **RPAP — A Boon to Rural Minnesota**
James K. Heid, M.D. ... 826

PEDIATRICS — **Television and Children — A Physician's Guide**
Robert Devney, M.D. and Robert W. ten Bensel, M.D. ... 833

PROSPECTIVE MEDICINE — **Role of Prospective Medicine in Health Care**
Thomas A. Fenger, Ph.D. ... 841

BOOK REVIEWS ... 807

MINNESOTA MEDICINE — **Statement of Ownership** ... 808

CONTINUING MEDICAL EDUCATION ... 774, 790, 792, 804, 843

CLASSIFIED ADVERTISEMENTS ... 845

INDEX TO ADVERTISERS ... 844

Volume 62:11
Pages 767-848

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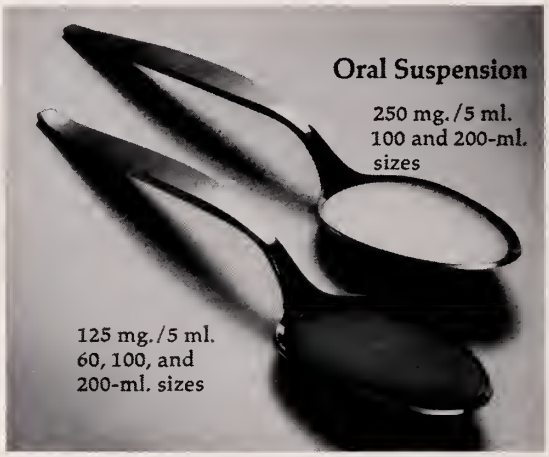
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President's Letter

SERVING AS your President has been a learning experience which I value highly and feel obliged to share.

In the area of professional liability insurance, certain basic facts have been made evident to me. First is the simple truth that if a loss occurs as a result of a professional liability claim, that loss is paid by physicians. A second reality is that the insurance carrier operates as any legitimate business in that its prime concern is to be certain that premium income is sufficient to cover loss from claims, plus a given percentage for expenses and profit. Quality of practice or legitimacy of claims is of concern only in how the bottom line of profit and loss is affected. In all fairness, however, they do not in their organization possess sufficient knowledge about medical care to enable them to be effective in risk management and loss control in more than a very general way. Physicians, themselves, are the only persons in a position to recognize a practice which may invite a professional liability claim. Physicians are also best qualified to recognize claims which have legitimacy and, therefore, should be settled promptly and generously and which claims are not legitimate and should be vigorously defended.

We are all aware that something in our current social structure and psyche has created an atmosphere of litigiousness. This is regretable and disturbing. Yet it is a fact which curses will not cause to disappear. It is up to physicians to deal with the reality in whatever way is appropriate. As individuals, we can help by keeping good records and maintaining an interest in the patient as a whole person.

As an organization, the MMA is actively involved in attempting to deal with the problem of professional liability. Your colleagues now sit on an insurance underwriting committee with representatives of the St. Paul Companies. Another joint committee with physician representatives from the various specialties scrutinizes in detail the specifics of cases in which malpractice has been claimed so that the St. Paul Companies and their legal advisors may have independent, off-the-record opinions as to the legitimacy of the claims. Further, the association has engaged the services of Johnson and Higgins Company as consultants. Together they, the MMA and the St. Paul Companies have joined in presenting risk management seminars at various county medical societies. Also, Johnson & Higgins have been helpful in assisting us to negotiate for you, with the St. Paul Companies. I believe that this effort has brought dollar rewards which far exceed the dues which we pay for membership, not only in the MMA but the AMA as well. Non-members, of course, also benefit.

Additionally, in response to direction from the House of Delegates, we are currently studying the possibility of creating our own captive professional liability insurance company. At present, more cannot be said about that effort, but I will try to keep you informed as new information accumulates.

The MMA provides a myriad of services and is involved in numerous areas which affect the economics of your practice. I believe that we *should* do more and could, were it not for budget constraints. The budget can be enlarged by increasing dues or adding new members. We prefer the latter. It, therefore, behooves each active member to look about him for colleagues who have not yet joined our ranks and then attempt to educate that person that he/she has a social obligation which can be honorably discharged at the very minimum by becoming a dues paying member of the county, state and the AMA.

Frank E. Johnson

Frank E. Johnson, M.D.
President
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CULLEY C. CARSON III, M.D.* and REZA S. MALEK, M.D.*

Appendicovesical fistula is an uncommon condition that may be missed because of the confusing history. The fistula usually occurs in young males and is associated with chronic urinary tract infection. Diagnosis is based on cystoscopic findings that may be confirmed by a retrograde study. Treatment by appendectomy is usually successful.

Fistulous communication between the appendix and the bladder is rare; it accounts for only about 1% of enterovesical fistulas. Appendicovesical fistulas usually occur after unrecognized acute appendicitis in males who are between 10 and 40 years of age. The fistulas usually are neither suspected clinically nor demonstrated by the usual diagnostic techniques.

This report describes a patient with an appendicovesical fistula who presented with a typically confusing history and nearly underwent an unnecessary renal operation before the fistulous communication was recognized.

Case Report

A 23-year-old man presented with an 11-month history of recurrent urosepsis. He had no previous urologic problem. However, on detailed questioning, he described an episode of pain in his right flank and abdomen which had occurred nine months previously, with subsequent dysuria, frequency, high temperature, and chills. The episode had been treated with rest in bed and antibiotics. The patient continued to have malaise and low-grade fever, but eventually he became asymptomatic and afebrile and returned to work in six weeks. An excretory urogram had revealed a "cyst" in the right kidney which was considered to be the nidus of the urosepsis. He had three further episodes of low-grade fever and dysuria during the next

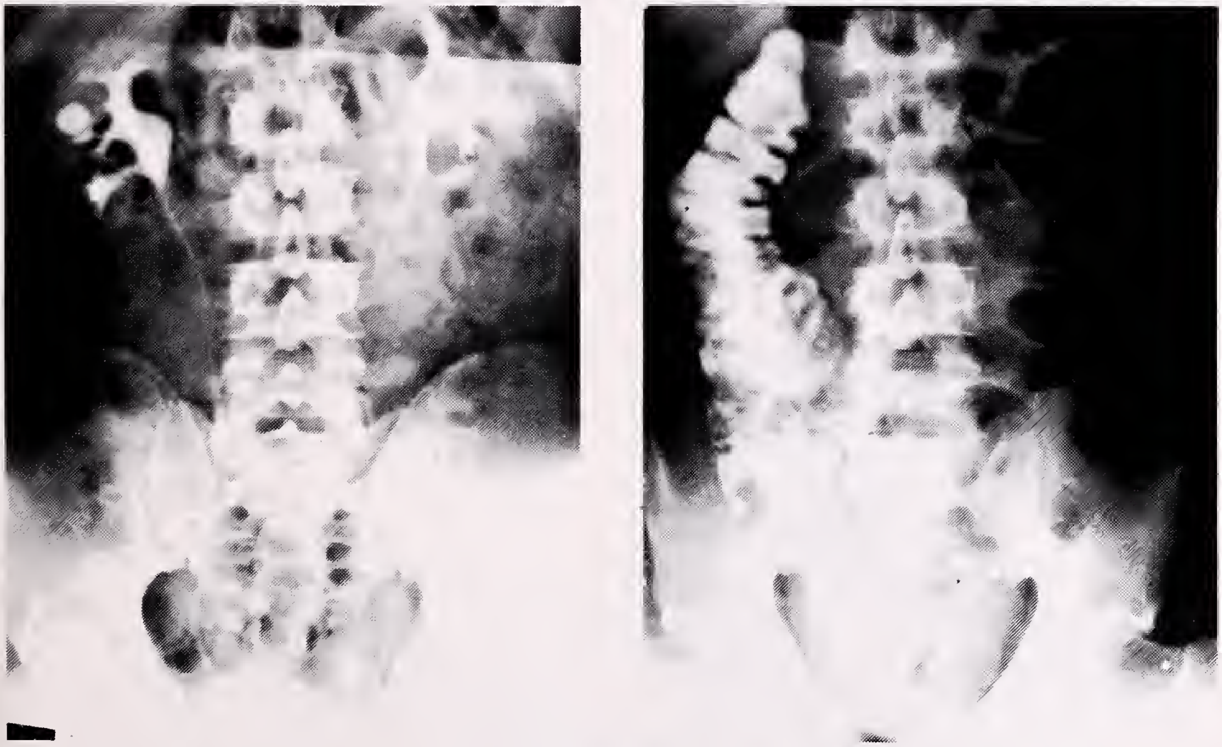

Figure — (A-left) Excretory urogram demonstrates caliceal diverticulum in right kidney. Remainder of upper urinary tract and bladder outline were normal. (B-right) Cecum and right colon have been opacified via a ureteral catheter that has been passed into appendicovesical fistula under cystoscopic guidance.

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nine months and was again treated with antibiotics.

On admission, he was afebrile and results of physical examination were normal. Routine laboratory test results were negative, except for the finding of pyuria and microhematuria. Urine culture revealed *Klebsiella* urosepsis. The excretory urogram disclosed only a 1.5-cm, nonobstructed caliceal diverticulum in the upper pole of the right kidney (Figure A). Findings on proctoscopy, barium edema study, and voiding cystourethrography were all normal. After treatment of the *Klebsiella* urosepsis, cystoscopic examination under anesthesia revealed subacute inflammation of the posterior bladder wall and a small crater located posterolateral to the right ureteral orifice. A 5-F catheter was advanced 2 cm into this opening, and contrast medium was instilled. Subsequent films disclosed contrast medium in the cecum and ascending colon, with the suggestion of an appendiceal stump forming the connection (Figure B). At laparotomy, dense pelvic adhesions and a small curled appendix adjacent to the right side of the bladder dome were found. The appendix, which contained a large obstructing fecalith, and the fistulous tract were excised, and the vesical wall and cecum were closed.

Postoperatively, the patient's recovery was uneventful and the Foley catheter was removed on the eighth day. One year later, the patient was asymptomatic and uninfected, without any antimicrobial therapy.

Discussion

Eighty-one cases of appendicovesical fistula have been reported in the literature; of these, only 17 were reported in detail.[1] The fistulas usually occur in patients who are between the ages of 10 and 40 years, and men predominate by a ratio of nearly four to one.[2] This male predominance reflects the location in the female of the uterus, which forms an effective anatomic barrier between the large bowel and the bladder. The most common cause of appendicovesical fistula, as in the present case, is acute appendicitis in which either the patient has not sought medical attention or the condition has been misdiagnosed. Appendicovesical fistula is usually found in patients with an intrapelvic appendix. After the inflamed appendix ruptures, a periappendiceal abscess forms and may erode into the nearby bladder. The inflammatory process rarely perforates the thick bladder wall; more commonly, it loculates around or perforates the more contiguous, thinner-walled rectum.[1,2]

Symptoms usually are suggestive of acute appendicitis and may include vague lower abdominal distress, cystitis, hematuria, pneumaturia, or fecaluria.[1,2] Occasionally, chronic urosepsis is the presenting symptom. The most common organism recovered from the urine is *Escherichia coli,* but any member of the colonic flora may be involved.

Diagnostic procedures should include excretory urography, retrograde cystography, and cystoscopy. Localized cystitis and bullous edema are the most common cystoscopic findings. Feces and mucus in the bladder or a frank fistula, usually on the right side of the bladder dome, are occasionally encountered. Any overt fistula, apparently blind tract, or exudative area within the bladder should be probed, catheterized, and evaluated with a retrograde study. Frequently, a fecalith acting as a ball valve permits a fistula to remain quiescent, with only episodic urinary tract infections. In these cases, retrograde studies can quickly establish the appropriate diagnosis and expedite appropriate surgical treatment.

Treatment consists of appendectomy, with removal of the fistulous tract and a cuff of bladder around the fistula. Catheter drainage and appropriate antibiotic therapy should be continued for at least seven days after the operation.

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AMA Committee on Accreditation of Continuing Medical Education

John S. Welch, M.D., Rochester, Minnesota, has been appointed to the AMA Committee on Accreditation of Continuing Medical Education. The new committee will make recommendations to the AMA Council on Medical Education regarding procedures and standards for the evaluation and recognition of state medical societies to accredit organizations and institutions providing intrastate CME.

Dr. Welch, a Mayo Clinic surgeon, has served as Chairman of the MMA Committee on Medical Education since 1975.

Necrotizing Fasciitis

A Lethal Infection

RICHARD F. KYLE, M.D.* and RAMON B. GUSTILO, M.D.*

Necrotizing fasciitis is a potentially lethal infection caused primarily by beta hemolytic streptococcus and staphylococcus. There have been four cases of this infection in the last two years at Hennepin County Medical Center. Two patients died. Treatment requires early recognition, immediate surgical debridement, and institution of parenteral antibiotic therapy.

NECROTIZING FASCIITIS was first described by Dr. Joseph Jones, a Confederate Army surgeon, in 1871.[4] He noted that the "skin of the infected parts turned green, blue, grey, or black, and then melted away." The first case to be supported by bacteriologic data was reported as necrotizing erysipelas by Pfanner in 1918 and was shown to be caused by beta hemolytic streptococcus. Meleney in 1924 reported on 20 cases which he called streptococcal gangrene and concluded that the main feature of this disease was subcutaneous undermining.[5] Rea and Wyrick reported on the largest series of cases in the recent literature and stated that necrotizing fasciitis is the preferred terminology when the most significant manifestation of the infection is extensive necrosis of the superficial fascia with resultant widespread undermining of surrounding tissues and extreme systemic toxicity regardless of the specific bacteriologic etiology.[7]

Necrotizing fasciitis is a potentially lethal infection which usually starts from some minor trauma (80% of cases reported by Rea) and causes necrosis of superficial fascia with widespread undermining and systemic toxicity. Hemolytic streptococcus and staphylococcus are the organisms cultured in 90% of the cases reported in the literature. Toxins consisting of cellular components from pathogenic bacteria become fixed in the local area by combining with dermal connective tissue, accounting for the extensive undermining. Toxins are also dispersed systemically, accounting for the generalized toxicity.

Case Reports

Case 1 – (Figures 1,2,3)

A 25-year-old female was seen at a Minneapolis Hospital with a small infected lesion on her right fourth finger from a needle prick. She complained of right shoulder pain and was admitted in the evening with a diagnosis of a rotator cuff tear. Overnight she became extremely toxic and developed brawny edema of her right shoulder and right anterior chest wall. She was transferred to Hennepin County Medical Center in shock. Her temperature was 105.8°, pulse 150, and blood pressure 0/40, hemoglobin 12.1, white blood cell count 4,900 with 97% polymorphonuclear leukocytes, sedimentation rate 8, calcium 5.3, and BUN 28. Gram stains of fluid taken from the lesion revealed gram positive cocci in pairs and chains, and later cultures grew many beta hemolytic streptococci — Group A and moderate staphylococcus coagulates positive. She was immediately

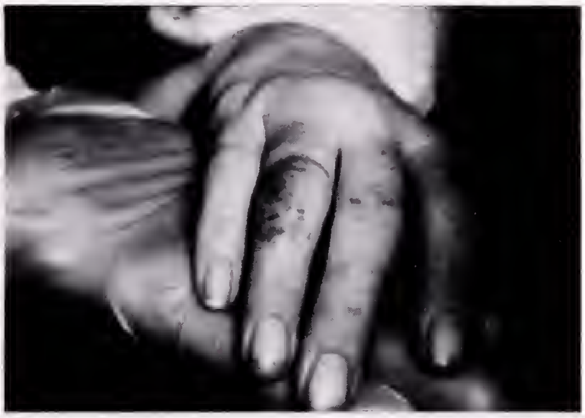

Fig. 1 (Case 1) a 25-year-old female with a small infected lesion on her right fourth finger from needle prick was admitted to a hospital with the diagnosis of a rotator cuff tear because of pain in the shoulder.

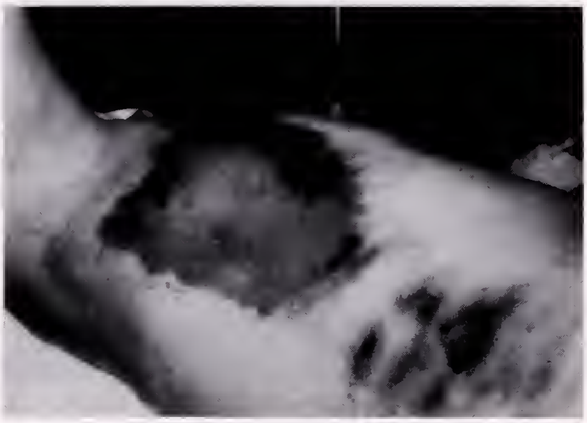

Fig. 2 — Overnight she developed brawny edema of her right axilla and anterior chest wall, became shocky, and was transferred to Hennepin County Medical Center.

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started on volume replacement and vasopressors. One gram of Solu medrol was given intravenously. She was given Na penicillin, 6 million units every four hours and gentamycin, 10 mg every twelve hours. Sodium bicarbonate was administered to counteract acidosis and Lasix to maintain urine output. She was thereupon taken to surgery. Debridement of all necrotic tissue in the anterior aspect of the shoulder and chest wall was carried out. Despite the use of pressor agents as well as rapid plasma infusion, her blood pressure could not be maintained. The patient suffered a cardiac arrest and died on the operating table.

Case 2

A 53-year-old male was hospitalized ten days after a fall during which he suffered a laceration of the dorsal aspect of his right elbow. Past medical history revealed that the patient suffered from adult onset diabetes mellitus, mild hypertension, and chronic alcoholism. Five days prior to admission, the patient developed swelling and drainage from the injured elbow. This became progressively worse until he sought medical advice. On physical examination there was a ragged appearing 4 cm laceration over the dorsal aspect of his elbow that could be quite easily probed beneath the subcutaneous tissues for a distance of 12 cm both proximally and distally. There was a profuse serous drainage without odor from the lesion. His blood pressure was 148/86, pulse 90, temperature 99°, hemoglobin 14.5, white blood cell count 14,500 with 78% polymorphonuclear leucocytes, sedimentation rate 39, and calcium 7.7. Gram stains of drainage from the lesion revealed gram positive cocci in chains and pairs. Later cultures of this material grew many beta hemolytic streptococci — Group A and a few staphylococcus coagulates positive.

He was immediately started on fluid replacement, Keflin 2 grams intravenously every four hours, and sodium penicillin, 6 million units every four hours. He was taken to surgery and the subcutaneous tissue from the wrist to the axilla was found to be undermined and had a grey, shaggy appearance. The entire area of darkened skin about the laceration was excised. The dorsal and ventral aspects of the arm from the wrist to the axilla were incised for drainage. The patient's blood pressure and temperature, which had deteriorated to 90/50 and 104° just prior to surgery, returned to normal within six hours following surgery. Wound cultures returned the following day growing beta hemolytic streptococcus and staphylococcus coagulates positive, both sensitive to Oxacillin. The Keflin was discontinued and the patient was started on Oxacillin, 2 grams every six hours. He was also maintained on Penicillin 6 million units every four hours. The wound was inspected the next day for any evidence of subcutaneous dissection, but none was found. A limited amount of debridement was carried out. His clinical course improved, and two days later he was returned to the operating room for partial wound closure. Two days following this, he underwent primary skin grafting over the area of resected tissue. He was discharged nine days after his admission and maintained on Dicloxacillin for an additional five days. His recovery was complete, and he regained full use of his upper extremity.

Case 3

A 59-year-old male was admitted to an out-of-state hospital for treatment of gangrene of the second toe on his right foot. The patient's past medical history included adult onset diabetes mellitus, angina pectoris and alcoholism. Within 24 hours following his admission, the patient developed severe cellulitis of his entire thigh which spread up his right flank into the right axilla and shoulder. He was treated with erythromycin, penicillin, and gentamycin, but no surgical debridement. His temperature rose to 105°, and he went into septic shock at which time he was transferred to Hennepin County Medical Center. On physical examination he had brawny edema of his right axilla and upper arm. He had severe cellulitis of his entire right leg. His blood pressure was 70/52, pulse 160, temperature 105°, hemoglobin 9.6, white blood cell count 13,000 with 94% polymorphonuclear leucocytes, sedimentation rate 20, and calcium 6.9. He was immediately started on vasopressor agents and given Solu medrol 1 gram intravenously. He was started on sodium Penicillin 6 million units and Oxacillin 2 grams intravenously every four hours. He was also started on Chloramphenicol 1 gram intravenously every twelve hours. A specimen aspirated from his right arm revealed gram positive cocci in pairs and chains on gram stain. Later cultures grew out beta hemolytic streptococci — Group A. The patient was immediately taken to surgery where the entire axilla and upper arm region were incised and drained. The patient developed seizures immediately after surgery, and a spinal tap revealed beta hemolytic streptococci in the cerebral spinal fluid. The patient remained comatose after the seizure, went into renal failure, and died of cardiac arrest three days following surgery.

Case 4

A 63-year-old male developed spontaneous swelling of the dorsal aspect of his right hand. His past medical history revealed that he had adult onset diabetes and angina pectoris. Because of the increased swelling over a two day period, the patient sought medical advice and was admitted to the hospital. Clinical examination revealed a 3 x

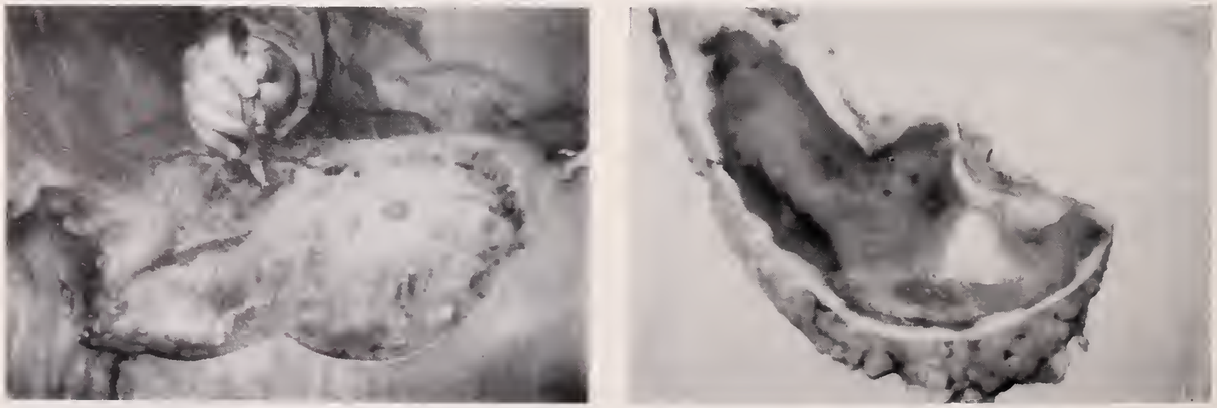

Fig. 3 — Immediate supportive therapy, surgical debridement, and antibiotic therapy were instituted. Subcutaneous dissection with overlying necrotic fat and skin was found and all necrotic tissue excised. The therapy was instituted too late, and she died 18 hours after her admission to the hospital from a seemingly insignificant injury.

4 cm area of erythema and swelling over the mid dorsal aspect of the right hand. There was no obvious open lesion and the area was moderately tender. The patient had full use of his hand, although he suffered some pain with full flexion of his fingers. The admitting temperature was 102°, pulse 90, blood pressure 130/88, hemoglobin 10.1, white blood cell count 25,000 with 88% polymorphonuclear leucocytes, sedimentation rate 18, and calcium 8.6. An aspirant of the infected area revealed gram positive cocci in chains on gram stain. Later cultures grew beta hemolytic streptococci — Group A. The patient was placed on sodium Penicillin, two million units every two hours and Oxacillin, one gram every three hours intravenously. He was then taken to surgery where incision and drainage of the lesion revealed extensive undermining of the subcutaneous tissue about the infected area. There was a shaggy grey appearance to the subcutaneous tissue and a serous drainage. All areas of necrotic tissue were removed and the wound was irrigated and packed open with gauze soaked in normal saline. The patient responded well to therapy and his temperature returned to normal within 24 hours. He was given a 14 day course of parenteral antibiotic therapy, and the wound inspected and debrided daily until it was covered with a skin graft on the tenth day after the initial surgery. He recovered after the surgery completely and retained full use of the hand.

Discussion

Necrotizing fasciitis is an uncommon, but potentially serious, infectious process. For this reason, it must remain high on our list of differential diagnosis with any infected-appearing lesions. The majority of cases start from seemingly insignificant trauma, such as a puncture wound or abrasion. It has also been known to occur after tooth extraction, surgical procedures, and intramuscular injections.[1,2,6] Drug addicts are particularly susceptible because of their use of unsterile needles.[6] Patients become rapidly toxic despite little pain, and they may at times seem quite apathetic about their condition. This toxicity seems quite out of proportion to the insignificance of the observable lesion. On close examination of the lesion, there is subcutaneous undermining and serous exudate. There is usually no gas or gross pus, although on rare occasions gas may be present due to gas forming gram negative organisms. The hemoglobin may be low, and the white blood count is markedly elevated usually with the preponderance of polymorphonuclear leucocytes. Conversely, the sedimentation rate is usually only slightly elevated. A gram stain reveals many gram positive cocci, although gram negative rods may also be present. Usually the blood culture is positive. The calcium may be low. Most authors feel this results from saponification of the calcium with subcutaneous fat. In the cases presented, all of these elements were present. In young patients without additional medical problems, the mortality rate has been reported to be around 30%, while in older individuals with diabetes mellitus or severe atherosclerotic disease, the mortality rate has been reported as high as 80%. The most important factors in treatment are immediate surgical debridement and parenteral antibiotic therapy. We recommend intravenous sodium Penicillin, 6 million units every four hours, and intravenous or intramuscular Gentamycin 5 mg per kilogram of body weight per day in two divided doses. Renal function must be monitored closely. In addition, fluid replacement and transfusion may be necessary. The patient must be returned to surgery and additional debridement carried out as necessary.

Differential Diagnosis

Erysipelas presents as an erythematous area with sharply defined borders and is very painful. There is no undermining and systemic symptoms are mild. Bacterial synergistic gangrene is slow in onset and usually occurs in an operative wound. It is painful and has only limited undermining.

Gas gangrene usually occurs in contaminated wounds and is a deep infection involving muscle as well as subcutaneous tissue. There is purulent drainage rather than serous drainage, and a foul odor. Crepitation may be palpated and gram stain shows gram positive rods.

Summary

Necrotizing fasciitis is a potentially lethal infection which many times starts with some seemingly insignificant injury. It is rapid in onset and causes extreme systemic toxicity. There is diffuse subcutaneous undermining with a serous exudate from the lesion. Gram stains show gram positive cocci, although gram negative rods do not rule out this clinical entity. Treatment consists of immediate surgical debridement and institution of parenteral antibiotic therapy along with systemic support. Treatment must be immediate and cannot wait for the return of cultures.

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Liver Injury
Secondary to Radiation Therapy for Breast Cancer

NEIL R. HOFFMAN, M.D.*

The treatment of breast cancer is currently undergoing changes and modifications, causing in at least certain subgroups, increased survival. Modern therapeutic programs require multiple physicians with varied specialty knowledge to interact with one another in planning treatment programs. It is not uncommon to see patients treated for breast cancer to receive surgery, radiation therapy and chemical therapy. It is therefore, essential that physicians treating patients with this disease become familiar with these three treatment modalities, as well as their complications. This paper presents a patient with radiation induced liver disease and discusses the findings as well as the clinical complications as they apply to therapy.

RADIATION DAMAGE to liver tissue is not a well appreciated disease entity, as usually efforts are made to shield this organ during delivery of therapy to the surrounding tissues. Radiation dose tolerances for liver tissue have been defined, and are generally felt to be 3000 rads, delivered over a period of three to four weeks.[1,2] Those patients in which tolerance has been determined, have had radiation sensitive malignancies, e.g., lymphoma, seminoma, where therapy was devised to include the liver. Usselman,[3,4], and Gilday[5], in following such patients, have shown the sharply demarcated areas of reduced uptake on liver scans, corresponding to the areas of liver injury. They, as well as others, have reported the regenerative capacity of the adult liver following radiation damage, as well as the poor regenerative capacity of damaged liver in children. The following case is presented to show the typical finding in radiation induced liver disease, as well as showing the important task of differentiating such changes from tumor progression.

Case Report

A 40-year-old female underwent a right radical mastectomy in September 1977. The lesion was present in the lower central quadrant of the right breast. The pathologic diagnoses of this tumor was a multifocal infiltrating ductal carcinoma, with invasion into the skeletal muscles of the chest wall. Five of twenty-nine axillary nodes were positive for metastatic disease. Estrogen binding studies done on a sample of tumor tissue were negative. Additional medical history revealed the patient had insulin dependent diabetes mellitus, with retinopathy and neuropathy.

Laboratory studies revealed a normal preoperative bone scan as well as normal liver function studies. Because of a somewhat medial lesion, and chest wall invasion, radiation therapy to the internal mammary nodes, chest wall, and supra clavicular areas was started. The patient underwent 15 treatment days for a total of 3580 rads to the above areas delivered by a 4 MEV linac machine. Following a three week recovery period she was started on adjuvant chemical therapy, consisting of Cytoxan, Methotrexate and 5-Fluorouracil (CMF). As the patient was to receive her second course of chemotherapy, she complained of nausea and lethargy. Chemotherapy was postponed even though the physical examination was negative. Serum Calcium, BUN and blood sugar were found to be normal as well as her liver chemistry profile and complete blood counts. Due to persistence of symptoms the patient was admitted to the hospital for evaluation, five weeks after completion of radiation therapy.

Hospital Course

Patient was found again to have a normal serum calcium, as well as normal renal function tests. Liver function studies were now noted to be abnormal (Table). Her serum SGOT was 293 (N=0-40), LDH was 357 (N=0-200) and her gamma glutamyl transpeptidase was 128 (N=0-40). A liver scan done with 99M Technetium S.C. showed poor distribution of activity in the entire upper portion of the liver, suggesting an infiltrative, metastatic process (Figures 1 and 2). A computerized scan of the liver area showed no filling defects, and was felt to be normal (Figure 3). A needle biopsy of the liver, under direct visualization, using the CT scanner, showed no evidence for

TABLE

Serial Liver Function Studies

Laboratory tests	11/77	12/9/77	12/30/77	2/2/78
SGOT	25	21	293	49
LDH	185	186	357	240
ALK. P'TASE	68	176	138	187
GGT	20	38	128	72

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*Clinical Assistant Professor of Medicine, University of Minnesota Medical School and Hennepin County Medical Center, and the Department of Internal Medicine, Mount Sinai Hospital, Minneapolis, Minnesota.

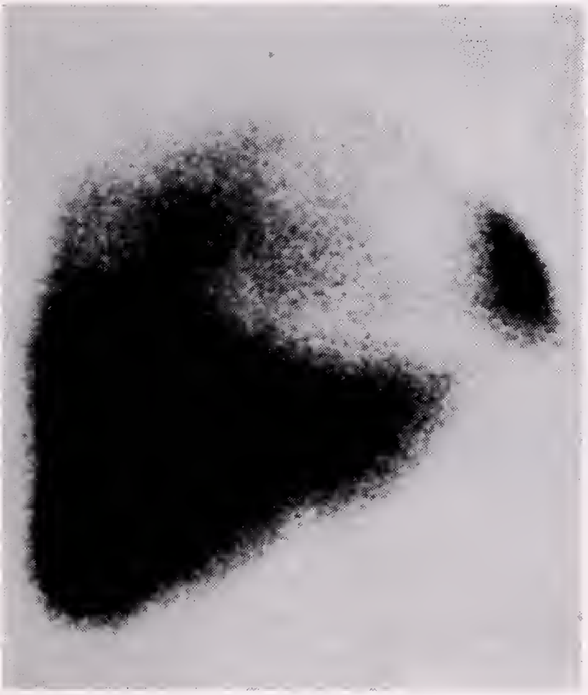

Fig 1 — Anterior Radionucleotide Liver Scan.

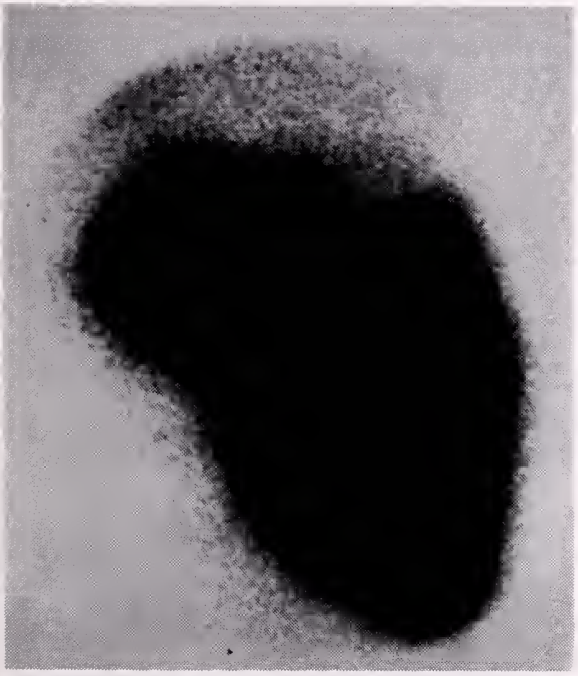

Fig 2 — Right Lateral Liver Scan.

malignancy. Chemotherapy was deferred, and approximately six weeks later, her liver function studies started returning towards normal. SGOT was now 49, LDH was 200 and GGT was 72. At this time the nausea and lethargy had regressed and patient reported a feeling of normal health.

Discussion

Radiation damage to the liver may be due to a direct effect of radiation to the parenchymal cells, or via the blood supply[6]. Histologically the liver becomes sclerotic, and there is internal proliferation of the central veins, with secondary congestion. Atrophy of liver cells also occurs in the irradiated portion of the liver[7]. Radiation damage to the liver usually presents with a sudden increase in liver size. The liver is usually tender to palpation, and ascites may be present. Liver function studies, primarily the SGOT, GGT and alkaline phosphatase may show rather sudden abnormalities. The serum bilirubin is generally normal as jaundice is not a feature of this entity. Liver biopsy in radiation treated areas will usually show after four-six weeks, partial congestion with atrophy and necroses of liver cells. Bleeding may be difficult to control, therefore, biopsy if indicated, is best done with a thin needle. In the adult, clinical symptoms, e.g. nausea, lethargy and liver tenderness will regress by the sixth month, and permanent liver damage with doses under 3500 rads over four weeks is unusual.

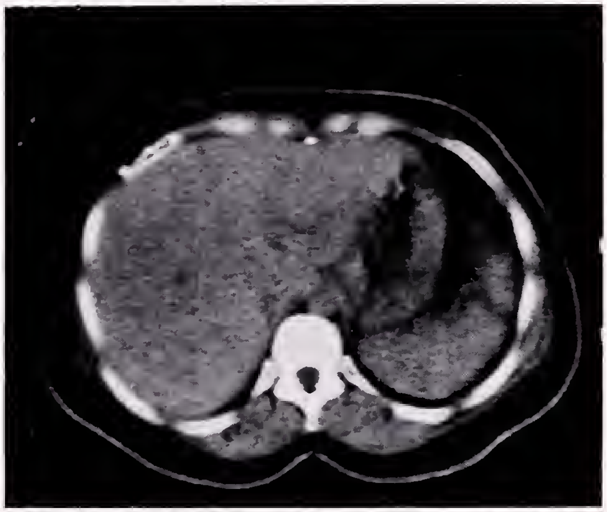

Fig 3 — C-T Scan of the Liver Showing Slightly Enlarged Liver with no Evidence of Metastatic Disease.

Post operative radiation therapy as an adjunct in the treatment of breast cancer is generally delivered so as to spare the liver tissue. Treatment, when indicated, is to decrease the possibility of local recurrence, and does not affect the development of distant metastases. For this reason the field size is usually limited, and not extended inferior enough to include the liver. It is important to recognize the possibility of radiation induced liver disease, and even radiation hepatitis in patients treated by radiation therapy to the chest wall. A pre-treatment liver scan will help delineate this finding, as well as the development of hepatic metastases. Since breast cancer has a high predilection for hepatic infiltration, recognizing the difference between radiation damage and metastases, may alter further therapy. Since many cytotoxic agents are cleared and metabolized by the liver, adding chemical therapy to an already ailing liver may be hazardous.

Since earlier recognition, and treatment of breast cancer is becoming more important, and since this is now involving multiple specialty modalities in the field of medicine, it is now becoming necessary for all physicians to recognize these additive complications to therapy. Only as we communicate better between the treating specialties, will we hopefully continue to improve the survival statistics in this disease.

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COVER PHOTOGRAPH

"Superior North Shore"

View from the high Palisades Cliff of the Lake Superior North Shore taken on one of Dr. Earl Henrikson's many trips to get fall color pictures. In the distnace is the well-known Shovel Point reaching far out into the lake.

De. Henrikson, Minneapolis surgeon, won MINNESOTA MEDICINE'S Outstanding Cover Award for the November, 1978, cover of the Journal "Waiting for Breakfast." The Editors are proud to be able to again publish one of his excellent photographs on the cover of MINNESOTA MEDICINE.

Reporting of Maltreatment of Patients

Minnesota Statute 626.555 requires that unless it is clearly evident that the patient's injury is the result of an accident, the health provider having knowledge of the injury has the responsibility to report the case to the Minnesota Commissioner of Health. Such incidents should be reported promptly to the Minnesota Department of Health's Division of Health Systems, Survey and Compliance, telephone number (612) 296-5420. A written report should follow. Any person knowingly and willingly violating this law is guilty of a misdemeanor.

Kenath H. Sponsel, M.D.

Dr. Kenath H. Sponsel, Minneapolis surgeon, won the Southern Minnesota Medical Association's award for excellence in scientific exhibit at the 1979 meeting of the Association in St. Paul. The Editors congratulate Dr. Sponsel.

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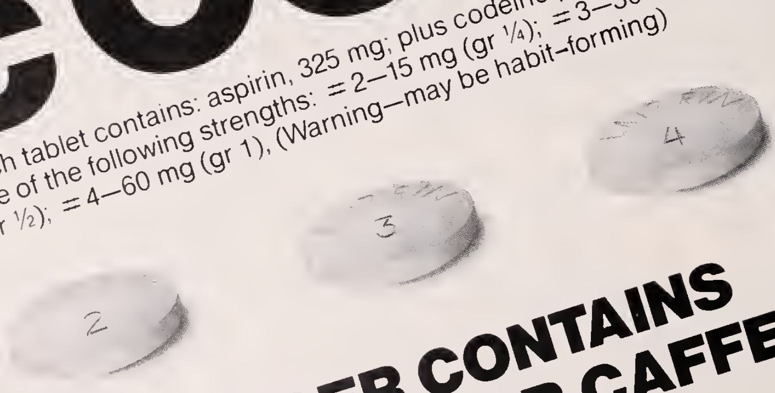

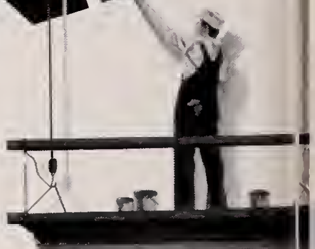

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Proximal Tibial Metaphyseal Fractures in Children

A Complication

RICHARD J. AADALEN, M.D.*

Proximal tibial metaphyseal fractures in children can produce a significant genu valgus as a result of what appears to be a rather innocuous fracture. Because of the benign appearance of the fracture initially, careful attention to alignment is occasionally neglected. At other times, even with what appears to be a healed fracture with satisfactory alignment, a progressive valgus may develop. Three illustrative cases are presented. Possible mechanism of deformity is reviewed and steps to avoid deformity are suggested. Treatment of the resultant deformity is discussed.

THREE CHILDREN with genu valgus following fracture of the proximal tibial metaphyseal area were referred to me in the past two years. While this is a recognized complication of this fracture,[4] it is not a common fracture. Because of the benign appearance of the Xray at the time of fracture, the potential for deformity is not always recognized and this possibility may not be discussed with the parents in the course of treatment of the fracture. The three cases seen recently are presented in hopes of increasing awareness of this fracture and its propensity to produce deformity.

Case Reports

Case 1

This 19-month-old girl was referred for knock-knee deformity thirteen months after the fracture in Figure 1. She had been treated in a long leg cast with the knee flexed forty-five degrees and the deformity was not appreciated until the fracture was healed and the child stood with the knees extended. No reduction of the fracture had been done. She was followed for eight months with no improvement in deformity and, therefore, corrective osteotomy was performed. Figure 2 shows the preoperative and postoperative alignment on standing AP Xrays.

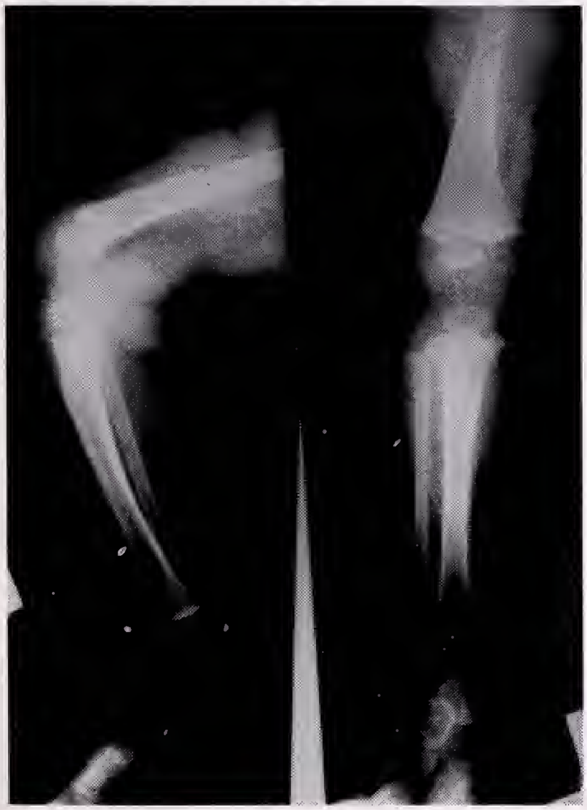

Fig. 1 — Initial Xray of patient. (Case #1.) at time of fracture.

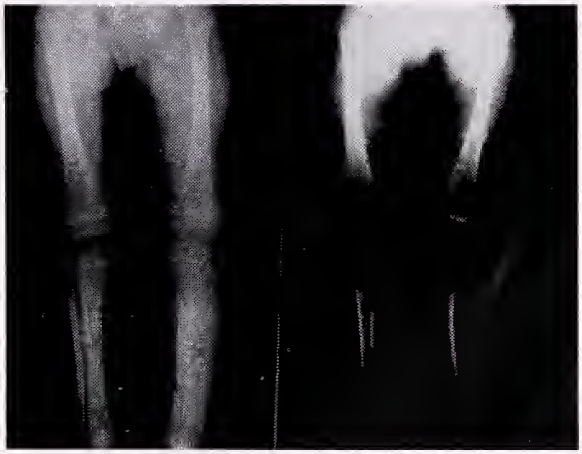

Fig. 2 — Xrays of (Case #1.) before and nine months after corrective osteotomy.

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*Minneapolis, Minnesota.

Case 2

The child sustained the fracture in Figure 3 at nine months of age and was treated with a long leg cast with forty-five degrees of knee flexion. No reduction was attempted. After cast removal only a slight valgus deformity was noted. He was referred at fifteen months of age with eighteen degrees of valgus deformity as seen in Figure 4. He was treated with brace support (Figure 5) for thirteen months. Very little improvement was noted and corrective osteotomy is planned.

Case 3

This 20-month-old white female sustained a proximal metaphyseal greenstick fracture of the tibia at age twelve months. Figure 6 shows the x-ray appearance six weeks post fracture, and Figure 7 shows the appearance when seen by me eight months following fracture with fifteen degrees of valgus deformity. A corrective osteotomy was done with over-correction to three degrees of varus (Figure 8). Xrays seven months postoperative showed good alignment (Figure 9).

Discussion

Tibial overgrowth and unilateral genu valgum as a potential sequelae of an undisplaced or minimally displaced fracture of the proximal tibial metaphysis in children was described by Cozen[2] in 1953. It is well known that after fractures of long bones in children, longitudinal overgrowth of the bone may occur. This overgrowth may occur without displacement of the fracture and is variable from patient to patient. Bisgard[1] and others have shown that when overgrowth occurs it may continue for six months and the greatest gain in length is in the first few months. In the fracture under discussion there is frequently fracture of the tibia with an intact fibula. The development of genu valgum has been attributed to overgrowth of the tibia with the fibula exerting a tethering effect.[6]

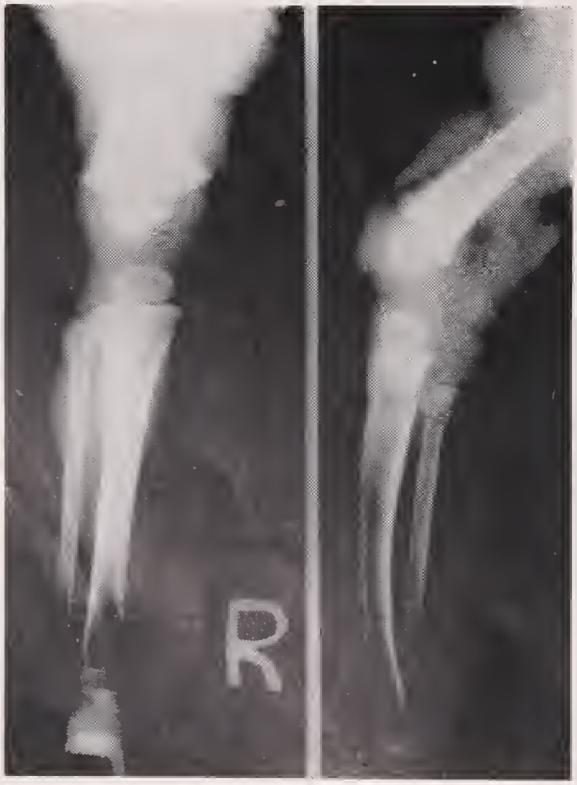

Fig. 3 — Initial Xray of patient (Case #2.) at time of fracture at age nine months.

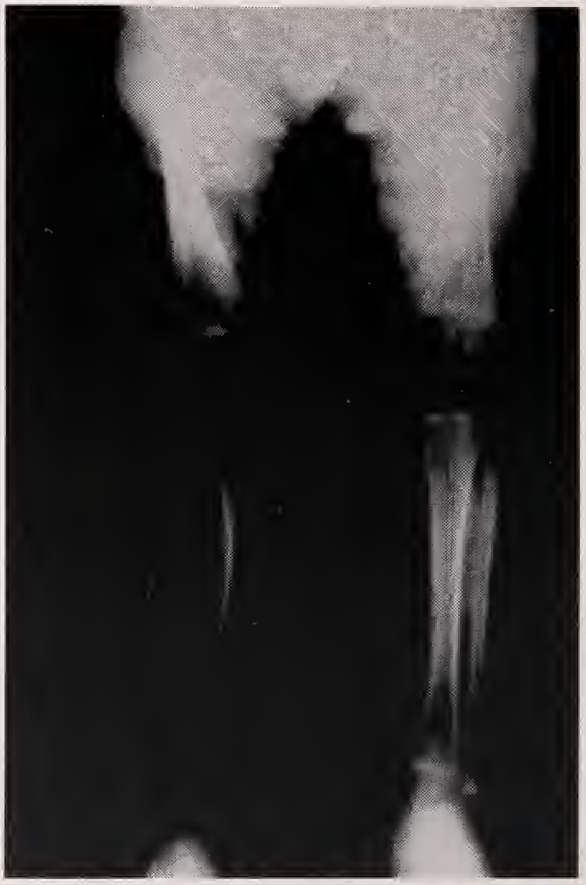

Fig. 4 — (Case #2.) Xray appearance of patient at age 15 months with 18° of valgus deformity.

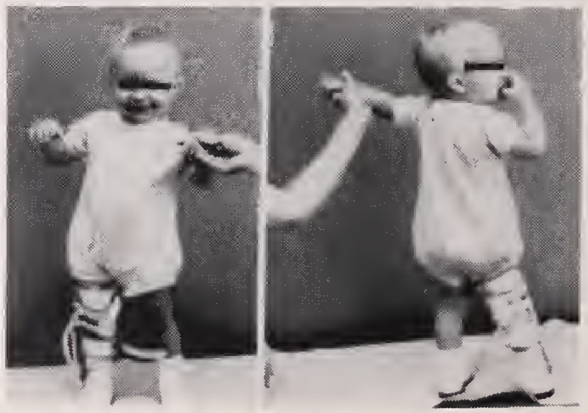

Fig. 5 — Patient (Case #2.) in lateral upright brace with medial knee cuff.

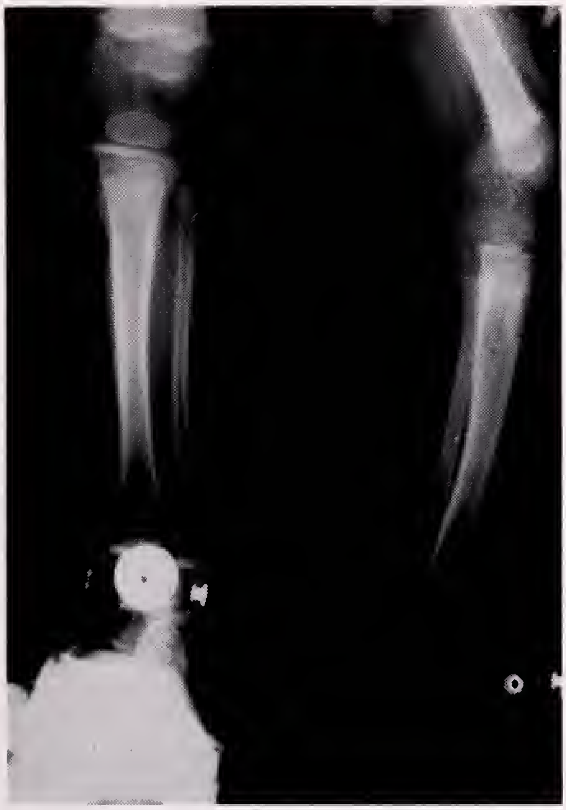

Fig. 6 — (Case #3.) six weeks post fracture.

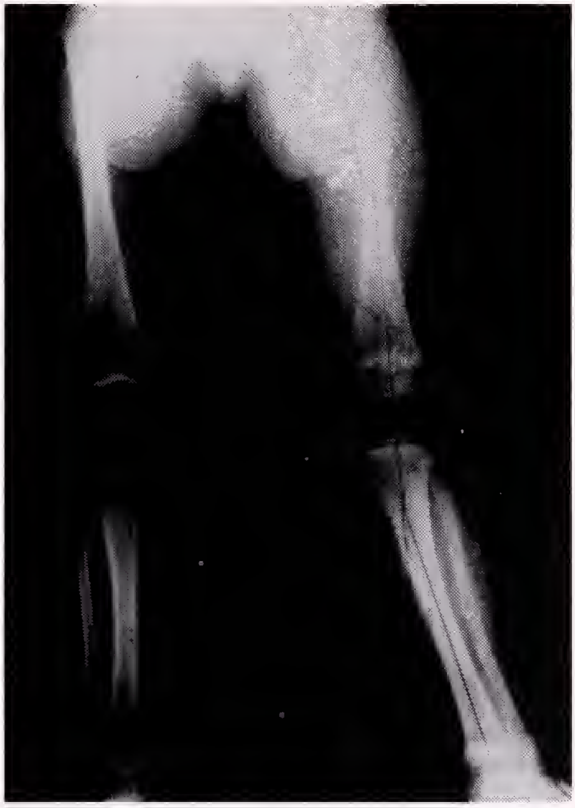

Fig. 7 — Patient (Case #3.) eight months post fracture showing significant valgus deformity.

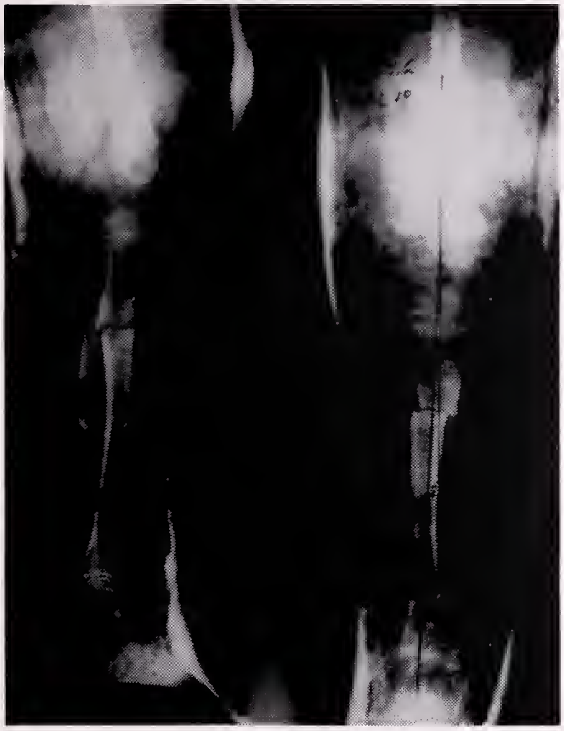

Fig. 8 — Patient (Case #3.) following corrective osteotomy.

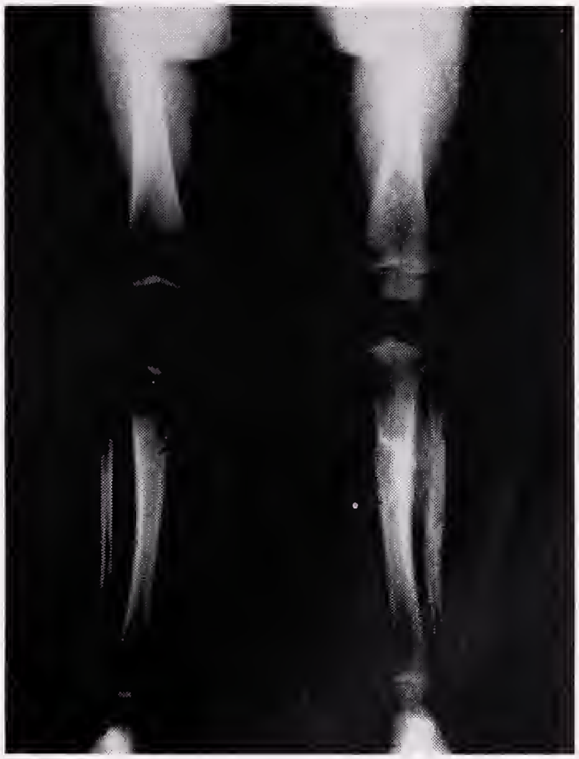

Fig. 9 — Patient (Case #3.) seven months postoperatively showing good alignment.

Ten cases of this deformity were reported by Jackson[3] in 1971. All were undisplaced except for some angulation, eight were greenstick fractures, and two were complete. The fibula was fractured in three and intact in seven. The average age of this group was 5.8 years with a range from 2.5 years to 12.0 years. The amount of valgus ranged from five to twenty-five degrees. Treatment was undertaken if the deformity was greater than fifteen degrees compared to the normal leg. Of the ten children, four required no treatment, three were treated with braces for eight to twelve months and improved, and three required osteotomy to correct the deformity.

Salter[5] presented twenty-one cases of this entity in 1975 and has not found bracing to be helpful in correcting the deformity. He recommends a closing wedge osteotomy if the deformity is severe.

Based on our review of this fracture and experience with the three cases presented the following recommendations are made.

Recommendations

1. Recognize this fracture as one with potential for delayed deformity.
2. Reduce any angulation present at the time of fracture and apply a long leg cast with the knee in extension so that deformity can be appreciated and followed during healing.
3. Warn parents of this possible sequelae even in an anatomically reduced fracture of this type.
4. Follow the child closely with standing x-rays for six to twelve months following healing of the fracture to detect deformity early.
4. When deformity does occur bracing may not correct the deformity. Corrective osteotomy may be required if deformity is severe.

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MINNESOTA MEDICINE

The Board of Editors of MINNESOTA MEDICINE invites the members of the Minnesota Medical Association to submit examples of their art work for publication on the cover of MINNESOTA MEDICINE. Color photographs, preferably transparencies, as well as photographs of paintings, drawings, sculpture, ceramics, jewelry, etc., are all welcome. There is no limit as to subject, but pictures of Minnesota or subjects topical to a month or season may have a slight advantage. Pictures will be returned if identified with the name and address of the maker. Please submit pictures to the Editor of MINNESOTA MEDICINE, 101 East 5th St., Suite 900, St. Paul, Minnnesota 55101.

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In stripping in the Figure for Dr. Stiegler's paper before running it in the September issue of MINNESOTA MEDICINE, the negative processors covered up four lines of Dr. Stiegler's copy. The Editors regret this and are now republishing the corrected paper below.

Septicemia and Pleural Effusion from Eikenella Corrodens

A Normal Mouth Inhabitant

PAUL STIEGLER, M.D.*

Eikenella Corrodens, normal mouth inhabitant, can cause local and distant infections resulting from dental manipulations. A patient is presented with septicemia and pleural effusions secondary to dental extractions.

LATELY INCREASED interest has been focused on the pathogenicity of a normal oral bacteria — Eikenella Corrodens. Previously known as Bacteroides Corrodens, this organism readily enters the blood stream after dental surgery and has been associated with many local and distant focuses of infection. A case is reported of a patient who developed E. Corrodens septicemia and pleural effusion after dental extractions. This would be one of the rare cases reported to have involved the lungs.

History

A 71-year-old white male presented to his local doctor with malaise, fever, chills, slight non-productive cough three weeks after having all of his upper teeth removed. Physical exam was negative except for mild labored respirations, temperature of 103°, and occasional right lower lobe rales. There was no adenopathy or organomegaly. There was no history of travel, medications, environmental lung exposures, weight loss, TB or allergies. Patient had a 60 pack year history of smoking. Also vocal cord carcinoma was treated with local excision and radiotherapy two years ago. Review of systems was entirely negative.

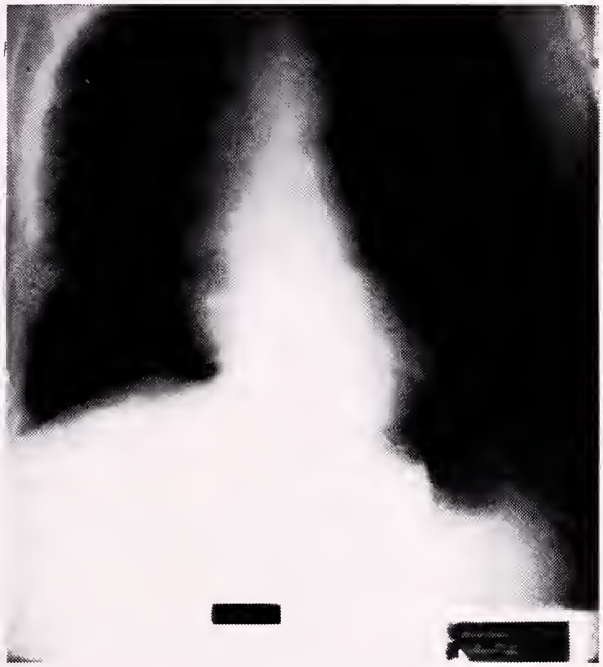
Chest Xray showed right lower lobe infiltrate, white blood count was 30,100 with left shift, and cultures of blood and sputum were negative. After trial of IV Penicillin the infiltrate resolved but fever and chills continued, despite changing antibiotics to Staphicillin and eventually a combination of Penicillin and Gentamicin. After two weeks in the hospital repeat CXR showed right pleural effusion, and patient was transferred to MMC.

On presentation patient was still spiking temperatures to 103° daily. Right lateral decubitus CXR showed right pleural effusion. Erythrocyte sedimentation rate was 131 and PPD was negative. Pleural fluid showed exudate with 13,000 WBCs (50% PMNs) but cultures were negative.

One week later blood cultures from admission finally grew out Eikenella Corrodens in two separate bottles, one of which also grew a microaerophilic alpha strep non group A, B, or D. Sensitivities of the E. Corrodens showed resistance to both Penicillin and Gentamicin but sensitive to Ampicillin, Carbenicillin, Chloramphenicol and Tetracycline. Ampicillin and Carbenicillin were then started intravenously with rapid defervescence of fever and resolution of chills over the next two days. After two weeks of this therapy, antibiotics were changed to only oral Ampicillin, and patient was discharged. Repeat blood cultures on day of discharge were negative after 10 days.

Discussion

Eikenella Corrodens is a facultative anaerobic gram negative rod that has recently been found to be a primary organism in many different infections. A normal inhabitant of the mouth, E. Corrodens has been isolated in many abscesses resulting from human bites.[8] The organism was earlier named Bacteroides corrodens because it was thought it was a truly anaerobic organism. However, in 1971 Jackson et



Figure

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*Family Practice Hennepin County Medical Center, Minneapolis.

al,[13,14] proposed the organism to be transferred to a new genus Eikenella, in honor of M. Eiken who did the original studies on the organism in 1958.[11] The organism has a different DNA-base composition of bacteroides and hence the genus change. The name "corrodens" refers to the characteristic colonies formed on agar which show a depression or "corroded area" instead of a normal raised colony. The organism grows better in a CO-2 environment and has a smell like laundry bleach (hypochlorite). A fastidious organism — it usually takes at least 48 hrs. to grow, and, as seen in our case, sometimes up to a week.

The organism has now been associated with many different infections, including cellulitis[3] osteomyelitis,[3] brain abscess,[9] endocarditis,[10] abdominal abscesses, and even liver[6] and pancreatic,[7] abscesses. The cultures are usually pure but it has also been grown occasionally with non A B or D streptococcus. Interestingly in our patient one of the blood cultures of E. Corrodens was accompanied with this streptococcus. The significance of the strep was shown by Brooks et al.[2] when evaluating abscesses of E. Corrodens in drug addict patients using Methyl phenidate. They injected rabbits subcutaneously with Methyl phenidate and E. Corrodens, but no abscesses formed. However, when adding streptococcus to the above mixture significant abscess formation occurred.

Antibiotic sensitivity to E. Corrodens is usual to Penicillin, Ampicillin, Carbenicillin, Tetracycline, and chloramphenicol. High doses of Aminoglycosides are needed and therefore should not be used. Resistance to Cephalothin is variable and marked to Methacillin. Of clinical importance is the marked resistance of Eikenella to Clindamycin which is usually very affective against anaerobic infections. Interestingly, our organism was resistant to both Penicillin and Gentamicin.

Therefore, as we have seen, Eikenella corrodens, known habitant of the mouth and upper respiratory tract has been implicated in many varying infections. This case was presented to show a new variant of the clinical picture so far seen with Eikenella. Although the culture from the pleural fluid never grew out Eikenella, the positive blood cultures and the clinical picture in this patient with the timing of the oral surgery seem to fit for a resultant pneumonia from septicemia by the Eikenella. The history, pathogenesis, clinical picture and treatment have been discussed and now it remains for us to think of this organism in infections which may be associated with previous oral manipulation.

Summary

A 71-year-old smoker presented with malaise, fever, chills, and productive cough three weeks after multiple dental extractions. Chest Xray showed a right lower lobe infiltrate, a blood culture grew out Eikenella Corrodens — a facultative anaerobic organism normally residing in the mouth.

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Congenital Factor VII Deficiency

Safety of Surgery without Preoperative Transfusion

R. D. NIEDRINGHAUS, M.D.;* JOHANNES AAS, M.D.;* and J. B. SANFORD, M.D.*

Factor VII is required for hemostasis, and its deficiency may result in serious bleeding. When confronted with the necessity for intervening surgically, most physicians administer plasma transfusions to raise the level of Factor VII before undertaking the operative procedure. In some cases, the operations were safely performed without the preoperative transfusions. The present report documents an additional case of Factor VII deficiency safely operated on without preoperative transfusion.

FACTOR VII, ALTHOUGH historically not included in the "intrinsic" pathway for blood coagulation, is required for hemostasis, and its deficiency may lead to a serious bleeding diathesis. Factor VII is a Vitamin K dependent protein; its precursor molecule is synthesized by the liver. Factor VII's properties are characterized by the shortest half-life of all the coagulation factors. It is the coagulation factor most sensitive to coumarin therapy.[1,2]

The first patient lacking Factor VII was described in 1951.[3] In 1964 a series of 36 cases met the authors' criteria for true congenital Factor VII deficiency, and they summarized the characteristics, the physiology and genetics of this disorder.[4] In 1964 52 cases of Factor VII deficiency were reported.[5] In this series, the patients manifested epistaxis, bruising, intraarticular hemorrhage, gingival bleeding, or uterine bleeding. Gastrointestinal bleeding as a single entity was rare; if present, it was usually associated with gingival or nasal bleeding. Fourteen of their 52 patients had major surgical procedures. Five of the fourteen patients had no plasma transfusion prior to the surgical procedure. None of these five patients experienced abnormal bleeding.

This report documents a recent experience with a patient who had occult Factor VII deficiency and a major surgical procedure.

Case Report

A 62-year-old white man was admitted to another hospital in 1969 because of melena. His history at that time included two previous episodes of melena, both occurring early in his adult life; one of the episodes required a blood transfusion. In 1969 a hemigastrectomy was performed. Melena recurred in 1973, but the patient did not seek medical attention at that time.

In July 1976 another episode of melena brought the patient to St. Mary's Hospital. He had no abdominal pain. At the time of this admission, the patient said he had been a two-pack-a-day cigarette smoker for 30 years, and he drank two ounces of brandy per day.

Physical examination on this admission, yielded findings which were normal except for a pulse rate of 100/min., and the presence of a congenital defect of the toes (syndactyly of first and second toes) of both feet. A chest Xray and flat and upright films of the abdomen were normal.

Laboratory studies showed a hemoglobin level of 11.2 gm/100 ml; the white cell count and the differential white cell count were normal. A blood chemistry profile and urinalysis were normal. A stool specimen showed a 4+ response to a test for occult blood. Coagulation studies showed these results:

Prothrombin time (pt)	35 seconds
Prothrombin time (control)	12 seconds
Prothrombin time with:	
patient plasma (0.9 cc.)	
normal plasma (0.1 cc.)	12 seconds
Partial thromboplastin time	30 seconds (23-44 sec.)
Fibrinogen	310 mg. percent (170-410 mg. %)
Platelet count	202,000/cu mm.
Fibrin split products	Less than 10 ug/ml (Normal less than 10 ug/ml).
Bleeding time (Ivy)	2 minutes (Normal less than 6 min.)
Factor VII assay	3% (65-135%)
Factor V assay	100% (50-150%)
Factor X assay	120% (45-155%)
Coumadin assay	None detected (Bio-Science, Van Nuys, California)
Factor VII inhibitor assay	Negative (Mayo Medical Laboratories, Rochester, Minnesota)

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*The Duluth Clinic, L.T.D., Duluth, Minnesota.

Gastric analysis showed a one hour basal secretion of 7.4 meq/hr, pH 1.46 with 15.6 meq/hr after Histalog stimulation. Serum gastrin was 46 pg/ml (normal less than 300 pg/ml).

The patient's prothrombin time of 35 secs was unaffected by the intravenous administration of aqueous Vitamin K^1, 20 mg.

Esophagogastroscopy confirmed the presence of a Billroth II anastomosis with an anastomotic ulcer. A specimen taken for biopsy from the ulcer showed benign tissue.

One month after his discharge from our hospital, the patient was readmitted with another episode of melena. Esophagogastroscopy showed a bleeding anastomotic ulcer. Two weeks of medical therapy was followed by performance of a laparotomy at which time the Billroth II anastomosis was taken down and the jejunum closed. Additional gastric resection and a gastrojejunostomy were carried out, and the vagotomy was completed. No blood products were administered preoperatively, and no excessive bleeding occurred either during the operative procedure or in the postoperative period. The patient was discharged on the 12th postoperative day.

The patient was last seen thirteen months following his last discharge from our hospital. He had had no further bleeding. Inquiry into the family history disclosed no familial bleeding tendencies. His only living blood relatives, two brothers, aged 60 and 58 years respectively, both have normal prothrombin times. A Factor VII assay was done on one brother and showed 47 percent activity.

Comment

Our case of occult Factor VII deficiency illustrates the safety of a major surgical procedure performed upon a patient with this deficiency. Whether the earlier episodes of upper gastrointestinal bleeding were due to peptic ulcer disease or to Factor VII deficiency alone is not known.

Our experience and the experiences reported by others suggest that major surgical procedures can be safely undertaken in patients afflicted with Factor VII deficiency without raising the Factor VII level by pre-operative transfusion.

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Fall Seminar:	September 13-16, 1979 Brainerd, MN	
Spring Seminar and Annual Meeting:	April 19, 1980 L'hotel de France Minneapolis, MN	

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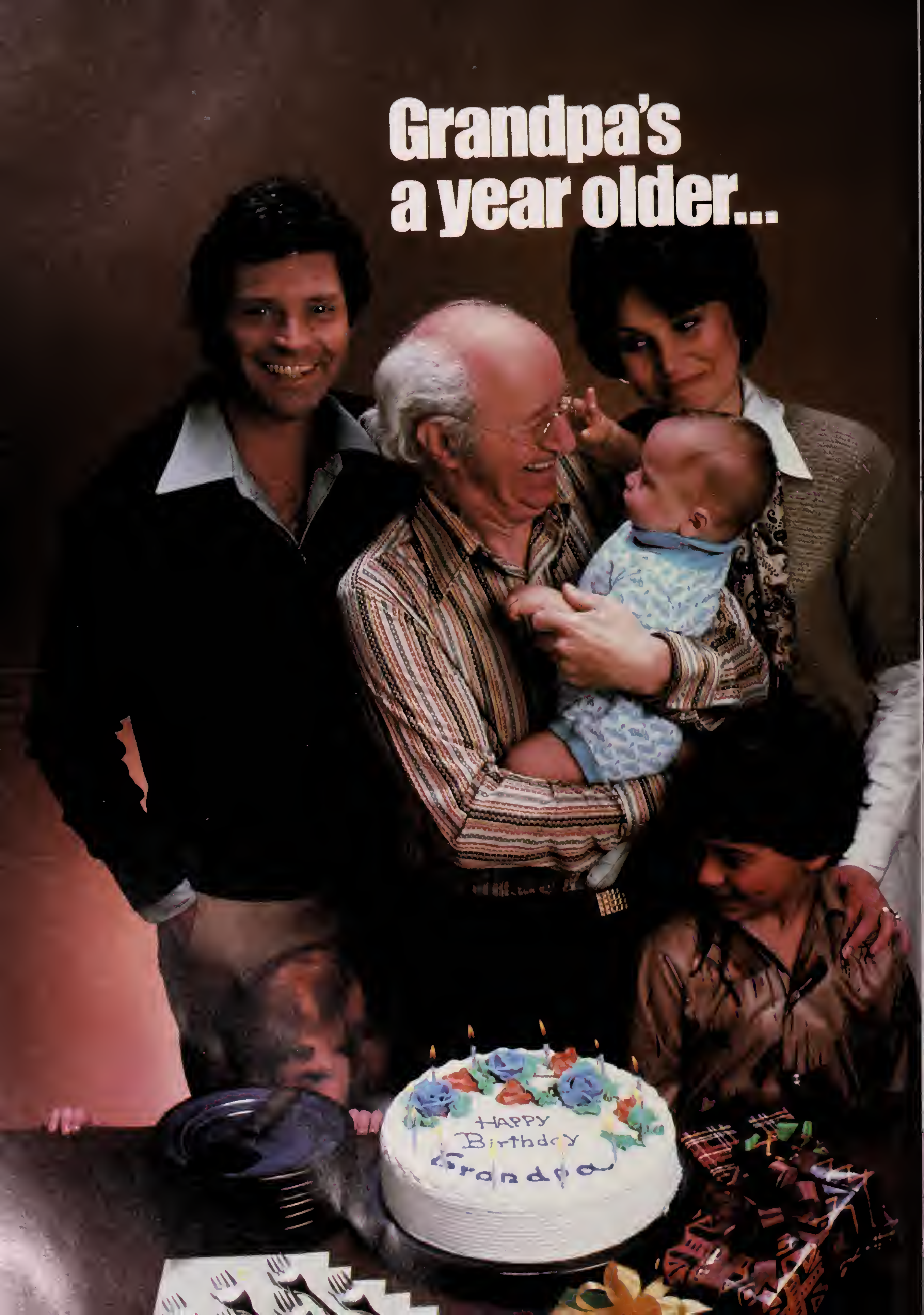
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INDICATIONS: PNEUMOVAX is indicated for immunization against lobar pneumonia and bacteremia, caused by those types of pneumococci included in the vaccine, in all persons two years of age or older in whom there is an increased risk of morbidity and mortality from pneumococcal pneumonia. These include: (1) persons having chronic physical conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders; (2) persons in chronic care facilities; (3) persons convalescing from severe disease; (4) persons 50 years of age or older.

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Children less than two years of age do not respond satisfactorily to the capsular types of PNEUMOVAX that are most often the cause of pneumococcal disease in this age group. Accordingly, PNEUMOVAX is not recommended in this age group.

PNEUMOVAX is not recommended for patients who have received extensive chemotherapy and/or nodal irradiation for Hodgkin's disease.

WARNINGS: *PNEUMOVAX will not immunize against capsular types of pneumococcus other than those contained in the vaccine (see table below).*

14 Pneumococcal Capsular Types Included in PNEUMOVAX

Nomenclature	Pneumococcal Types													
U.S.	1	2	3	4	6	8	9	12	14	19	23	25	51	56
Danish	1	2	3	4	6A	8	9N	12F	14	19F	23F	25	7F	18C

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained. Intradermal administration may cause severe local reactions.

PRECAUTIONS: Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX, except when, in the opinion of the physician, withholding the agent entails even greater risk.

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Children under two years of age may not obtain a satisfactory antibody response to some pneumococcal capsular types. Therefore, the vaccine should not be used in this age group.

ADVERSE REACTIONS: Local erythema and soreness at the injection site, usually of less than 48 hours' duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX (containing 14 capsular types) in 26 adults, 24 (92%) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination. Low-grade fever (less than 100.9°F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102°F has been reported.

Reactions of greater severity, duration, or extent are unusual. Rarely, anaphylactoid reactions have been reported.

NOTE: Administer subcutaneously or intramuscularly. *DO NOT GIVE INTRAVENOUSLY. DO NOT GIVE INTRADERMALLY.*

STORAGE AND USE: Store single-dose prefilled syringes and unopened and opened vials at 2-8°C (35.6-46.4°F). The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% added as preservative.

Use a separate heat-sterilized syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another. All vaccine must be discarded after the expiration date.

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Inject contents of syringe to effect a single dose.

Single-Dose and 5-Dose Vials

For Syringe Use: Withdraw 0.5 ml from vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

HOW SUPPLIED: PNEUMOVAX is supplied in 5-dose vials of liquid vaccine, for use with syringe only; in a box of 5 individual cartons, each containing a single-dose vial of vaccine; and in 5 single-dose prefilled syringes.

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Editorial

HMOs — Their Limitations and Role

ALFRED F. ANDEREGG, M.D. *

UNDER MY MEDICAL directorship, and as a practicing internist, a prepaid closed panel HMO was developed and built. I left that position three and one-half years ago to become an independent private practitioner in suburban Minneapolis. Currently I am Chairman of the Board of the Physicians Health Plan, an open panel HMO.

The physicians in Minnesota are now witnessing the widespread local and national press coverage given to Health Maintenance Organizations. It is important to recognize that the growth of these organizations is a slow one — except in Minnesota — despite the Federal Government's attempts to promote more operational plans. Now, the emphasis has been turned to the Independent Practice Association models. Two such plans are now either operational or near-operational in Minnesota; these are the Physicians Health Plan and the Metropolitan Area Prepaid Plan. Undoubtedly most physicians in our state will be influenced by HMOs in one way or another. They might participate or simply observe the results of the various types of this kind of medical care delivery system.

I believe that it is important at this time that physicians understand, also, what the HMOs do not do. First, this kind of delivery system has a limited role to play in the overall medical care system. A longstanding criticism of the HMOs has been that only the relatively healthy employed population in groups has been offered the cost saving program. Feeble attempts to dispel this stigma have not been convincing. The traditional medical system (and I don't buy the allegation "non-system" that is often used) continues to take care of the major medical needs of the total population including those living in rural and smaller cities, the senior citizens, welfare participants, the temporarily unemployed, disabled and individuals not qualifying as being part of a select group. Where would all of these people receive care if HMOs become a majority of patient care organizations? Would not there be loud protestations of "somebody do something." There is no evidence that HMOs can or even want to insure the continued medical services for all of these segments of the population.

Second, there are no dollars in the HMO system to support the critical needs of research and training that are so necessary to continue our foremost role in American medicine. In no way can our university hospitals deliver health care on the same cost basis as our community hospitals. Nor should they be expected to do so since their needs and costs are entirely different from the latter. To divest the medical schools of their opportunity to be full participants in our care system would lead to total tax support of the schools to be determined by the whim and mercy of the political forces.

Cost containment is the keynote today. The HMOs do focus upon this main component of health services simply because that without doing so they would be unable to survive. There is no question that operative HMOs have made physicians much more cost conscious. The I.P.A. model certainly has influenced participating physicians in the way in which they practice, and, for the first time, has given them some incentive to participate in cost saving practices. Whoever heard of a Blue Cross Plan or other insuring mechanism rewarding the physician directly by paying him fully for his professional services? There is no incentive for the practicing physician to go out of his way to save money for the usual insurance organizations. Certainly this is the time for the third party payers — Blue Cross, insurance companies and the government — to offer some carrots rather than the sticks of ridiculous regulations, punitive fees and loud cries of abuse that have not been proved. Commercial insurers and Blue Cross-Blue Shield Plans have a wide variety of deductibles, co-insurance and restrictions with the result that the individual physician does not know which financial arrangement is being used with each medical service. To be sure, all of the HMOs have instituted some restrictions in an attempt to safeguard their economic integrity, but these restrictions are uniformaly applicable and usually easily recognizable.

What is it that allows HMOs to provide a comprehensive program at a cost below that of a comparable commercial plan? The overwhelming key is a lower number of hospital days used per 1,000 enrollees. It does not result from a different patient mix or composition. To survive and flourish the prepaid plans discussed here must be competitive with other similar types of plans. The closed panel plans learned early that there was a lot of "fat" in the amount of health care hospital dollar expenditure. However, competitive forces have now reduced the amount of "fat" available.

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*Hopkins, Minnesota

Often omitted in discussions of this type is the value of the float (of money) inherent in receiving premium income in advance and having that money at work while the bills to be paid are deferred for as long as possible. A large amount of money can be made in the form of interest by playing this economic game. Administrative costs can be reduced since the employer group collects the premium income and sends it to the HMO in one large monthly payment. These ways of handling money are foreign to the traditional fee-for-service system.

There are a number of differences when one compares the closed (staff or group) model with the open (I.P.A.) model that can be reviewed at another time. My main concern at this time is that physicians should become informed as fully as possible about something that is going on in their midst. The movement will not go away. The Federal Government will push the development to illustrate that it is doing something about medical care costs. A national health plan undoubtedly will carve out a place for HMOs. It is important to understand the limited role that HMOs might play in the overall health care system of our nation.

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Legal — Ethical

Legal and Ethical Aspects of Pre-Employment Physical Examinations

RICHARD C. COHAN, M.D.[*][†]

IN THE COURSE of daily office practice, many physicians do pre-employment physical examinations for various companies. Because we were concerned about what a physician should reveal to an employer about the results of the preemployment examination, the Occupational Medicine Department of the St. Louis Park Medical Center explored the legal and ethical responsibilities of a physician doing pre-employment examinations. We recognize that this area will remain controversial and that there is no one definite answer to this question, but we offer these insights which may or may not stimulate your thoughts and reactions.

The legal aspects of the pre-employment examination were studied by a law firm which specializes in laws relating to health and human rights. Stated very briefly, the legal opinion was that it is unlikely that a true doctor-patient relationship is formed during a visit for a pre-employment physical examination when such an examination is conducted at the employer's direction. It was concluded that any type of information gathered from the pre-employment physical examination can be conveyed to the employer as long as the prospective employee has signed a release of information form that specifies what type of data will be sent to the employer. Thus it was recommended by the law firm that the prospective employee be asked to sign a form which releases the physician to send the entire copy of the history and physical to the employer. If such a release was signed by the employee, the physician legally could then send the actual notes or form on which the history and physical exam were recorded.

Turning to the ethical side of the question, we find that article seven from the Code of Ethical Conduct for Physicians Providing Occupational Medical Services[#] is helpful in this regard. It states: "Treat as confidential whatever is learned about individuals served, releasing information only when required by law or by over-riding public health considerations, or to other physicians at the request of the individual according to traditional medical ethical practice; and should recognize that employers are entitled to counsel about the medical fitness of individuals in relation to work but are not entitled to diagnoses, or details of a specific nature . . ." This code makes it very clear that as far as AOMA is concerned an employer is entitled to know only whether or not an individual is medically qualified to work and is not entitled to know about specific diagnoses. Although the law apparently allows greater transfer of medical information, those of us practicing occupational medicine as members of AOMA follow the AOMA code of ethics. At the present time at the St. Louis Park Medical Center, we just send a very short statement to the employer after the pre-employment physical examination stating one of three things:

1. The individual is qualified to work without restrictions; or
2. The individual is suitable for work with the following restrictions (listing the actual restrictions); or
3. The individual is not suitable for work at this time.

If we have an individual who has a history of back problems and should not do lifting over 20 pounds, we would check the second box and say that the individual was suitable for work with the restriction of not lifting over 20 pounds. Again, following the code of AOMA, we would not say whether the restriction was due to a back problem, cardiac condition, or a respiratory condition. We would just list what the restriction is and also we would ask the company to call us before a job change was made so we could be sure that the individual was physically qualified for the different job. There are a few medical diagnoses which the employer should be aware of: diabetes, epilepsy, and hemophilia. If one of these conditions is present I will explain to the employee that I think someone with whom he works should know about his condition in case of an emergency. If the employee agrees and signs the proper release of information form, I will pass this information on to the employer.

It is evident that legally we can probably release any information that is gathered during a pre-employment physical examination as long as the employee signs a proper release of information form, but ethically we are limited by the code of AOMA to telling an employer whether the prospective employee is qualified for the job. We endorse the code of AOMA and hopefully all physicians who perform pre-employment physical examinations will also abide by the code by just sending a summary of the pre-employment examination to the employer.

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[†] Member of American Occupational Medical Association's Committee on Ethical Practice in Occupational Medicine.

[#] Code of Ethical Conduct for Physicians Providing Occupational Medical Serivces, as adopted by the Board of Directors of the American Occupational Medical Association (AOMA) on July 23, 1976.

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Laboratory Letter

Infant at Risk for Early Onset Group B Streptococcal Infection

RALPH A. FRANCIOSI, M.D.[*]

Early Onset Group B Streptococcal Infection (EGBS) occurs within 48 hours of birth. The source of infection is colonization of maternal vagina with Group B streptococcus. The infected infant is usually premature (79%) and shows signs of hypoxia at birth (one minute Apgar ≤ 7). Respiratory distress is the presenting clinical sign of 90% of infected infants, whereas, the remainder show lethargy and hypotonia. Aids to diagnosis are: absolute neutropenia and/or an elevated immature/mature neutrophil ratio in peripheral blood; chest Xray showing hyaline membrane disease (HMD) or pneumonia. Sixty-four per cent died either of congenital bacterial pneumonia, sepsis or meningitis. The morbidity and mortality of EGBS can be reduced by earlier diagnosis and appropriate antibiotic therapy.

EARLY ONSET GROUP B streptococcal infection (EGBS) is defined as occurring within 48 hours of birth.[1] An infected infant is usually premature with the onset of respiratory distress shortly after birth that mimics hyaline membrane disease (HMD). The mortality rate is approximately 70 per cent even though many infants receive appropriate antibiotic therapy. This paper will review case reports of EGBS and characterize the infected infant.

Material and Methods

Case reports of EGBS since 1940 were located in the Index Medicus. Each article was reviewed for pertinent bacteriologic, clinical and post-mortem data.

Results

Group B streptococcal infection (GBSI) has been increasing in frequency since 1940.[1-27] The Table summarizes pertinent data from 328 cases. Two-thirds of the cases presented with respiratory distress syndrome (RDS) within twelve hours of birth. An initial chest Xray was interpreted in 85 per cent as either HMD or pneumonia. A pleural effusion was noted in 17 per cent of these infants. The peripheral white blood cell count was either $< 4500/\text{mm.}^3$ (absolute neutropenia) or had an elevated immature/mature neutrophil ratio (> 0.15) in all infants. Appropriate antibiotics were given to two-thirds of infants, however, only 18 per cent were treated within twelve hours of birth. Sixty-four per cent died within one week of diagnosis, one-half within seventy-two hours. The post-mortem examination determined the cause of death as congenital pneumonia, 91 per cent; or meningitis, 9 per cent. Three-fourths of the infants dying of pneumonia had HMD. The frequency of fatal infection was similar in the different types of Group B streptococci (GBS), i.e., 16/21 (75 per cent) type I, 7/11 (64 per cent) type II and 10/20 (50 per cent) type III.

Discussion

The frequency of GBSI has increased dramatically in the last decade with an incidence of 12,000 new cases in 1976.[28] Two-thirds of the cases present with clinical signs of RDS or shock within forty-eight hours of birth (EGBS). The remaining one-third present with clinical signs of meningitis or sepsis after one week of age (delayed onset).

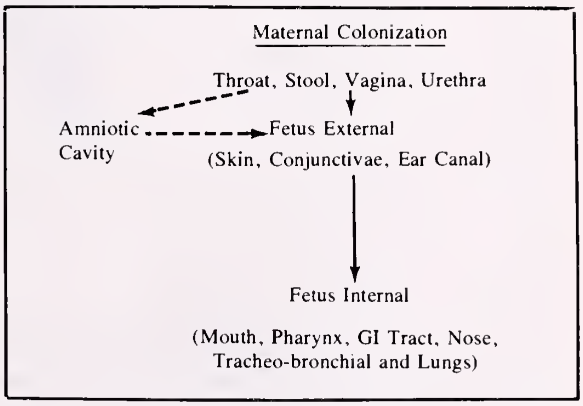
Maternal Colonization
Throat, Stool, Vagina, Urethra
Amniotic Cavity
Fetus External
(Skin, Conjunctivae, Ear Canal)
Fetus Internal
(Mouth, Pharynx, GI Tract, Nose, Tracheo-bronchial and Lungs)

Figure — Pathogenesis of EGBS.

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[*] Director of Laboratories, Children's Health Center and Hospital, Minneapolis, Minnesota.

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The Figure illustrates the pathogenesis of EGBS. The source is GBS in the maternal vagina which can colonize the fetus in-utero or during passage through the birth canal. Surface colonization can result in either non-fatal infections, e.g., pyoderma and conjunctivitis; or potentially fatal infection, e.g., pneumonia, sepsis or meningitis. The latter infections result from colonization of the pharynx, aspiration and sepsis.

This review indicates that the infant with EGBS is usually born prematurely with a low one minute APGAR score to a mother harboring GBS in her vagina. The subsequent course is the onset of RDS with a chest Xray showing either HMD or pneumonia in 90 per cent of cases. The peripheral white blood cell count has either absolute neutropenia or an elevated immature/mature neutrophil ratio. Ten per cent of cases present with lethargy and are diagnosed as meningitis. The mortality of EGBS is 64 per cent with all deaths occurring within seven days. The cause of death at autopsy is congenital pneumonia in 91 per cent and meningitis in 9 per cent. In retrospect, the infants dying with pneumonia had clinical symptoms of RDS whereas those dying of meningitis had lethargy, hypotonia and shock. The observation that HMD occurs in three-fourths of infants dying with pneumonia clarifies the clinical inability to separate most cases of EGBS from HMD.

Steigman, et al.[29] state that the morbidity and mortality of EGBS can be drastically reduced by early treatment with penicillin. This review supports their opinion by documenting that only 18 per cent of infected infants were given antibiotics within twelve hours of birth, although, two-thirds of cases showed clinical signs of infection. I would propose early penicillin treatment of infants born to mothers colonized vaginally by GBS if the infant is premature and has a one minute Apgar score ≤ 7. Antibiotic therapy can be started after the following infant cultures are taken: external ear canal, pharynx, blood and trachea. The clinical course can be monitored by observing for absolute neutropenia, elevation of immature/neutrophil ratio and either HMD or pneumonia on chest Xray. The clinician should be alerted for clinical signs of respiratory distress, lethargy, hypotonia and shock. If lethargy or hypotonia is noted, a spinal tap should be performed with culture. Penicillin therapy is continued for two weeks if the following positive cultures are reported: (1) external ear canal, pharynx and blood; or (2) blood; or (3) external ear canal and/or pharynx associated with Xray findings of pneumonia or HMD, or absolute neutropenia and/or elevated immature/mature neutrophil ratio; or (4) trachea; or (5) cerebral spinal fluid. In cases with organisms cultured from cerebral spinal fluid, Gentamicin can be used in combination with penicillin. Approximately 80 per cent of infected infants can be handled in the above manner, however, 20 per cent are born after 37 weeks gestation or with an Apgar score > 7. Immediately after birth these infants should have bacterial cultures taken from external ear canal, pharynx and blood. A white blood cell count and differential are done to document the presence of either absolute neutrophenia or an elevation in the immature/mature neutrophil ratio. A chest Xray will document the presence of either HMD or pneumonia. Clinical signs of respiratory distress, lethargy, hypotonia or shock are monitored. Following documentation of either absolute neutropenia and/or an elevation of immature/mature neutrophil ratio, HMD or pneumonia on chest Xray or the clinical signs mentioned, therapy with penicillin should be started and continued for two weeks. If lethargy or hypotonia are noted the cerebro-spinal fluid is cultured. If the cerebral spinal fluid culture is positive then an increased dosage of penicillin or combination with Gentamicin is indicated.

TABLE

	Cases of EGBS*
Premature	136/171 (79%)
Onset	179/284 (63%) ≤ 12 Hrs. 272/284 (96%) < 24 Hrs.
Xray	94/197 (48%) HMD 73/197 (37%) Pneumonia
RX	33/51 (65%) Treated 9/49 (18%) ≤ 12 Hrs.
Autopsy	72/79 (91%) Pneumonia 7/79 (9%) Meningitis
1' Apgar ≤ 7	39/50 (78%)
RDS	256/280 (90%)
WBC	39/45 (87%) < 4500 mm³ 19/45 (42%) ↑ I/M
Outcome	198/308 (64%) died 102/190 (53%) < 72 Hrs.
Maternal Culture	34/39 (87%)

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*Number of positive infants/total of infected infants.

↑ I/M = Immature/mature neutrophil ratio.

This approach should decrease the morbidity and mortality associated with EGBS. Additional studies are needed on the timing of maternal vaginal culture, e.g., 30 weeks gestation and delivery. The possibility of including an anal culture is raised since the rectal flora is the presumed source of vaginal colonization.

Summary

GBSI has increased in frequency dramatically over the last decade with an incidence of 12,000 cases in 1976. EGBS is acquired from GBS in maternal vagina and the infants show clinical signs of infection within forty-eight hours of birth. These infants are usually premature with one minute Apgar scores of ≤ 7 and 90 per cent develop RDS or 10 per cent present with lethargy and shock. Within seven days of diagnosis most infants die either of congenital pneumonia (91 per cent) or meningitis (9 per cent). Only 18 per cent are treated with antibiotics, yet, two-thirds demonstrate clinical signs of infection within twelve hours of birth. This suggests that earlier antibiotic treatment can reduce morbidity and mortality. I feel, however, that treatment should be limited to infants born to vaginally colonized mothers that have an Apgar score ≤ 7 at one minute, or exhibit the clinical signs, laboratory findings and Xray changes discussed.

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Indo-Chinese Refugees

Detection and Chemo Prophylaxis of Tuberculosis in Southeast Asian Immigrants

R. B.BREITENBUCHER, M.D. *

THE PREVALENCE of Tuberculosis among Southeast Asian immigrants is significant with 50 to 60% being Tuberculin Positive and some of them with active disease. In addition to the high incidence of Tuberculous infection, further cause for concern is the fact that indiscriminate and often ineffective use of Isoniazid (INH) in Southeast Asian countries has led to an increase in INH resistant disease. In contrast, the incidence of Tuberculosis in the United States has decreased to such an extent that most practicing physicians rarely encounter the problem. About 37,000 new cases are discovered annually in the U.S.A., and there are about 40,000 patients receiving therapy for active Tuberculosis. There are 200,000 to 300,000 persons with arrested disease. Only about 7% of the population are Tuberculin positive. It has become predominantly a disease of urban lower socio-economic groups.

Finding active Tuberculosis and Tuberculin reactors is a primary concern in dealing with the health problems of Southeast Asian immigrants, which has led to the development of specific policies in the Medicine Clinic at the Hennepin County Medical Center.

All Southeast Asian immigrants are given a Tuberculin test with intermediate strength Tween 80 purified protein derivative (PPD), unless there is a definite history of BCG received within the past year or a definite history of a previous positive Tuberculin test. All patients are requested to return to the Clinic 48 to 72 hours for reading the Tuberculin test. The determination as to whether or not the reaction is positive is made on the basis of induration. A positive Tuberculin reaction is one where the induration is 10 millimeters or more in diameter. Negative reactions show less than 5 millimeters of induration. Doubtful reactions are those with 5 to 9 millimeters of induration. In cases of doubtful reactions, a Tuberculin test is reapplied on the opposite arm to see if there is a "booster effect" which may result in a positive reaction. Since malnutrition and illnesses associated with immuno — suppression may cause false negative Tuberculin tests, consideration of these factors is made in interpreting results of the test.

Up to 21 years of age, if a patient is well nourished and otherwise healthy, no chest Xray is obtained if the PPD is negative. Over 21 years of age, chest Xrays are obtained regardless of whether the PPD is positive or negative. Yearly follow-up chest Xrays are obtained in those with positive PPD skin tests, among those who have fibrotic changes in the chest Xray, those with malnutrition, or those suspected of suppressed immunology regardless of PPD.

Although the French introduced BCG into several Southeast Asian countries, it is doubtful whether BCG has been administered in these countries on any significant scale for many years. A history of receiving BCG should not deter one from performing a Tuberculin test unless the BCG has been received within one year. After one year, those who have received BCG should have no more than a doubtful reaction from the BCG, and those with a reaction of 10 millimeters or more should be regarded as being positive for human Tuberculosis. BCG patients who have a PPD reaction of less than 10 millimeters are regarded as negative for Tuberculosis.

The guidelines for INH Chemoprophylaxis for Tuberculosis is the same in Southeast Asian immigrants as anyone else. This involves weighing the risk of developing active Tuberculosis against the risk of developing hepatic toxicity from INH. There is an age factor which is involved in the risk of liver disease among those receiving INH. Progressive liver damage is rarely observed under the age of 20 years. Between the age of 20 and 34 years, the incidence is 0.3%. The incidence rises sharply to 1.2% between the ages of 35 and 49 years, and nearly doubles to 2.3% at the age of 50 years and over. Pre-existing liver disease undoubtedly increases this risk. The daily use of alcohol probably also increases the risk. The liver disease that develops from INH is not the result of any particular manufacturing process or contaminant and is not predictable in any individual patient. Liver disease is more apt to occur in the first six months of therapy but

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may occur at any time. Any patient on INH should be warned to consult the physician immediately if anorexia, nausea, jaundice, dark urine, distaste for cigarettes, malaise, etc. develops. Although there is some controversy about this, the practice in this clinic is to routinely monitor patients receiving INH chemoprophylaxis with monthly SGOT levels. INH should be discontinued if there are clinical signs and symptoms of hepatitis, SGOT rises to 5 times normal, or if there are any symptoms suggesting adverse drug reaction (gastrointestinal, neuropsychiatric, hemotological, dermatological). In one study, there were no deaths or serious illness from INH in 1,000 patients managed with these guidelines. Contraindications to INH therapy include:

1. Previous Isoniazid associated hepatic injury.
2. Severe adverse reaction to INH such as drug fever, chills, rash, arthritis.
3. Acute liver disease of any etiology.
4. Pregnancy (prophylaxis should be started after delivery).

Prophylaxis is not contraindicated but requires special attention in those:

1. Currently using any other medication on a long-term basis.
2. Taking Diphenylhydantoin.
3. Daily alcohol users.
4. Previously having discontinued INH because of possible but not definitely related side effects.
5. With chronic liver disease.

In assessing the relative risk/benefit which may derive from INH prophylaxis, the figures relating to the risk of developing active Tuberculosis given in the Table are helpful, and should be balanced with the risk of hepatotoxicity. In general, considering benefits, risk, and cost, INH chemoprophylaxis should be given to the following:

1. All children with primary Tuberculosis,
2. All children who are household contacts of a person with active Tuberculosis regardless of PPD reaction,
3. Inactive cases of Tuberculosis who have not previously been treated with chemotherapy,
4. All Tuberculin positive adolescents,
5. Adult household contacts of persons with active disease (INH may be stopped after 3 months in adults whose PPD remains negative), and
6. Tuberculin positive adults who have additional conditions that increase the risk of developing active Tuberculosis (Table).

Treatment consists of 300 milligrams of Isoniazid and 50 milligrams of Pyridoxine daily for a period of one year.

TABLE

Incidence of Development of Active Tuberculosis per year

1. Household members and other close associates of persons with recently diagnosed tuberculosis.	**3.5-5%***
2. Newly infected persons (those with tuberculin conversion within previous 2 years)	**3.5-5%***
3. Persons who have had a recent contact with a person with active tuberculosis (under conditions which are not defined as close contacts as in 1.)	**0.5%**
4. Positive tuberculin reactors with findings on the chest Xray consistent with non-progressive tuberculosis disease, without positive bacteriological findings and without a history of adequate chemotherapy	**2.0%**
5. Positive tuberculin reactors in the following special clinical situations:	
a. Prolonged therapy with corticosteroids	**2.0%**
b. Immunosuppressive therapy	**2.0%**
c. Some hematological and reticuloendothelial diseases such as Leukemia or Hodgkin's disease	**2.0%**
d. Diabetes mellitus	**0.9%**
e. Silicosis	**2.0%**
f. Post-gastrectomy	**2.0%**
6. A person in the general population who is discovered to have a tuberculin positive test on a routine test	**0.07%**
7. Tuberculin negative persons	**0.002%**

*Figure probably applies only to the first few years after exposure.

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Book Reviews

STROKE AND ITS REHABILITATION. Edited by Sidney Licht. 562 pp. Elizabeth Licht, Publisher, New Haven, Connecticut, 1975. $20.00.

This is volume twelve of the library of physical medicine organized by Sidney Licht, ongoing since 1956 when the first volume, Electrodiagnosis and Electromyography, was published. Subsequent volumes have since appeared covering subjects such as: Therapeutic Heat and Cold, Exercise, Ultraviolet, Manipulation, Orthotics etcetera.

Volume twelve continues the series (with no end in sight) and impressively covers stroke from the physiatrists point of view. The purpose seems to be to provide physicians specializing in physiatry with a library of knowledge in the field. One might question the value of putting rapidly changing information as is the case in every field of medicine into hard covers. Medical books today are obsolescent on the day of publication with a half life of about two years. However they serve the useful purpose of building the base of knowledge omitted in specialized journal articles. Books thus should open the field to the early specialist and prepare him to follow his subject through other reading, meetings, and the like.

This book with sixteen authors necessarily is uneven. Dr. Licht is obviously fascinated by the history of his specialty and treats it in lively fashion occasionally I think going overboard in his enthusiasm going back to the Old Testament and prehistory to present ideas that are no more than conjectures. Murray Freed, Physiatrist at Boston City Hospital, wrote the chapter on surgical management of strokes. His account of the present status of this most difficult field, is well documented and will be informative to neurologists, internists, vascular and neurosurgeons who are involved in the selection and treatment of stroke and other cerebro vascular problems. He writes with the necessary disinterest in surgery in this controversial field of surgical interference.

Reuben Berman, M.D.
Editor Emeritus

THE PRACTICE OF PEDIATRIC NEUROLOGY by Kenneth F. Swaiman, M.D. and Francis S. Wright, M.D., Volumes I & II; The C. V. Mosby Co., St. Louis, 1975.

The authors, with the collaboration of 42 contributors, have compiled in these two volumes the most comprehensive, organized, and well-illustrated book in Pediatric Neurology to date. The book is divided into three sections; namely, Section I—emphasizes on the historical physical and laboratory examinations. This section further divides into Unit I: The Neurologic Examination During the First Two Years of Life; Unit II: Neurologic Examination of the Premature Infant; and Unit III: The Neurologic Examination of the Older Child. This division I find helpful.

Section II deals with "Symptoms and Signs of Neurological Diseases in Childhood." The authors in this section utilizing the child's symptoms and signs to develop differential diagnosis in a pediatric age group patient that presents with neurological signs and symptoms, which to us, is a practical approach for clinical problems. Furthermore, almost every chapter gives a brief but informative review of functional anatomy, physiology and pathophysiology before discussing the symptoms and signs. I find the knowledge and normal function with clinical signs and symptoms effectively integrated in this section. This will be helpful for a physician who is in busy clinical practice.

Section III: "Discussion of Neurological Diseases" provides the readers with a detailed description of the disease processes that affect the nervous system of children. Most of the chapters of this section are well written and informative.

The bibliography is quite extensive and up to date.

I enthusiastically recommend these two volumes for references in pediatric neurology for practicing physicians, as well as for medical students.

Frisca L. Yan-Go, M.D.
Rochester, Minnesota

NEW PARTS FOR OLD. The Age of Organ Transplants. John G. Deaton, M.D. 160 pages. Franklin Publishing Company, Inc. Palisades, New Jersey. 1974. Price: $7.40

The story surrounding the development of artificial organs and biological organ transplantation is one of the most exciting chapters in medical history. The entire field, for the most part, has progressed from science fiction status to significant reality in a scant twenty years. Solid accomplishments, characterizing these many achievements, have involved exposing some of nature's most grudgingly relinquished secrets and successfully overcoming some of her seemingly most unconquerable barriers. Small wonder then so many Nobel laureates are numbered among the victorious knights of science who valiantly prevailed in forcing open those tightly shut doors of intellectual darkness!

To tell this narrative in 160 pages, therefore, as the author has done, is a very courageous undertaking. He has done remarkably well in spotlighting the essential events embracing this saga and has presented the subject in an interesting, readable style. He ties together very well the threads of achievement, independently fashioned in diverse parts of the world, that were woven together over time and distance to comprise the fabric of the success story in the organ transplantation field. The author has managed to capsulize the accomplishments at both the fundamental and applied levels, recording historical achievements together with an analysis of significant basic data. He has blended, in perspective, the mundane with the esoteric in telling the story of artificial and biological organ transplantation progress.

.The author renders few judgments or opinions but seems to be content, for the most part, with simply being an accurate chronicler of events. On balance he has satisfied these objectives in a creditable fashion though the serious student of this field of science may feel there are some gaps to be filled and points to be contended for sake of strict accuracy.

Harold D. Kletschka, M.D.
Minneapolis, Minnesota

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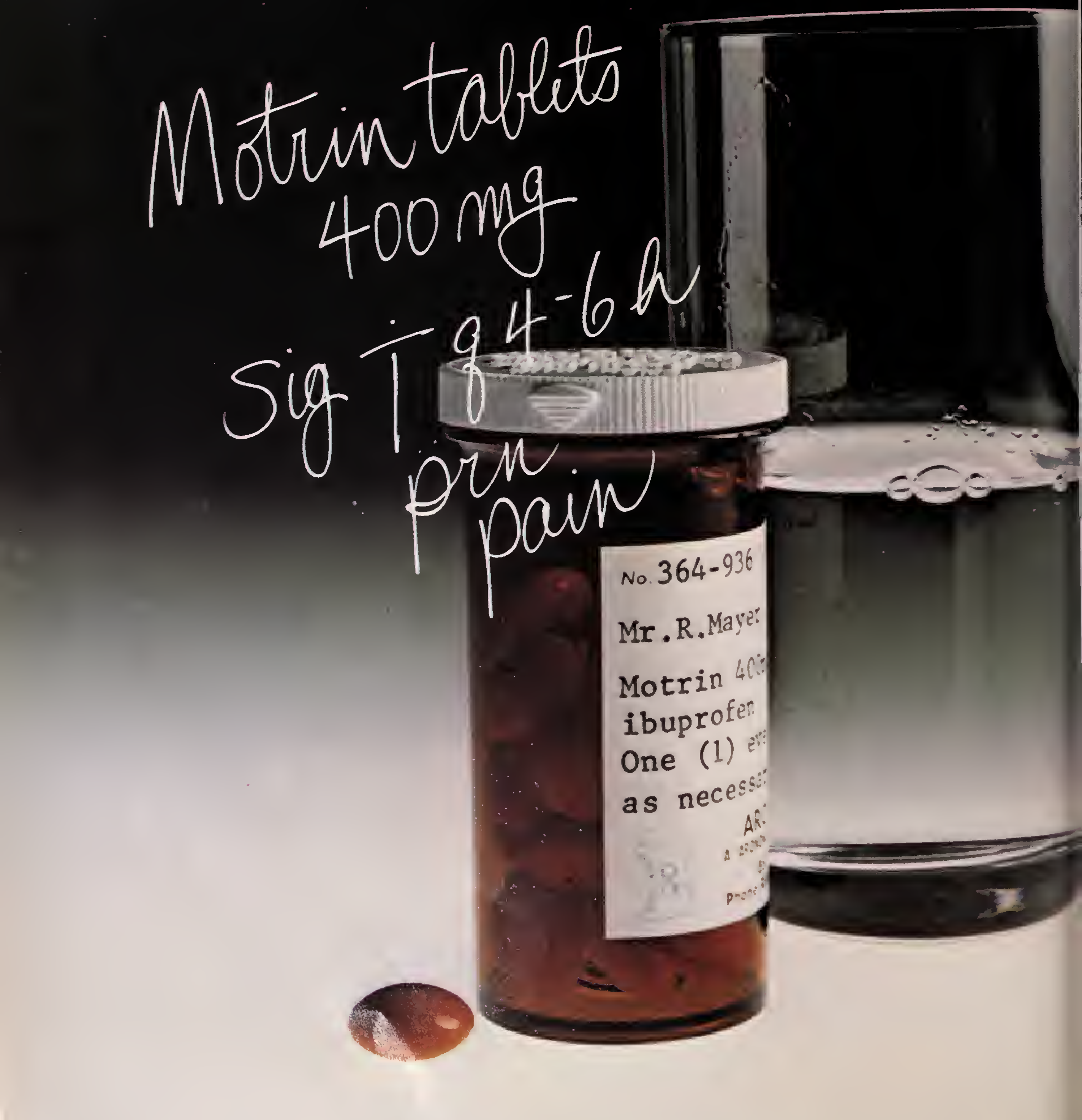
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Statistical significance		$p<0.02$	$p<0.01$	$p<0.05$	$p<0.02$	$p<0.002$

*0 = No relief 1 = Partial relief 2 = Complete relief

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Motrin® Tablets (ibuprofen, Upjohn)

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Relief of mild to moderate pain.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin:* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin is gastrointestinal (4% to 16%). This includes nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness,* headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

*Incidence 3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

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Special Article

Survival after Coronary Artery Bypass Surgery

Significance of Preoperative Left-Ventricular Function

CHARLES R. PETERSON, M.D.,* and H. K. HELSETH, M.D.*

The results of a follow-up study of 304 consecutive patients referred for coronary artery bypass surgery are reviewed. The disease profile of patients referred for surgery remained constant while there was a significant decrease in operative mortality during the eight-year study period. A major determinant of five-year survival was preoperative left ventricular function, since 50% of the operative deaths and 50% of the late deaths occurred in the 43 patients with poor preoperative left ventricular function. Five-year survival was 88% for all patients and 93% for patients with preoperative left ventricular ejection fractions over 0.45. There was no apparent relationship between late survival and recurrent angina after surgery. However, a relatively high graft patency rate in patients with the most significant coronary disease abnormalities may have protected these patients from late death despite recurrent symptoms.

THE GENERALLY ACCEPTED indication for coronary artery bypass surgery (CABS) is relief of angina pectoris that is not satisfactorily controlled with medical therapy. The effect of CABS on mortality from coronary artery disease remains controversial, but it is helpful to know the expected survival after surgery when considering this option of treatment.

This report describes 304 consecutive patients referred to one surgical group for CABS and the results of a one- to seven-year follow-up study on the first 228 of these patients. The significance of the following factors on operative and late survival are examined: early versus recent patient selection and surgery, extend of coronary disease, preoperative left ventricular function, recurrent angina pectoris after surgery, postoperative changes in coronary arteries, and bypass graft patency.

Patients and Methods

From January 1971 through December 1978, 304 patients evaluated by members of the Cardiology Section of the St. Louis Park Medical Center were referred to our surgical team for CABS. In December 1978, charts on these patients were reviewed. To obtain one- to seven-year follow-up on the 228 patients who had surgery before December 31, 1977, patients who had not been seen in 1978 after the anniversary

TABLE 1

Left Ventricular Function

Group	Ventriculogram	Ejection Fraction	LVEDP
Good	Normal wall motion	>0.55	<15mm Hg
Fair	Mild hypokinesia or <⅓ of wall akinetic or dyskinetic	>0.45	May be >15mm Hg
Poor	Diffuse hypokinesia or > ⅓ of wall akinetic or dyskinetic	<0.45	Usually >15mm Hg

LVEDP = Left ventricular end-diastolic pressure

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*Sections of Cardiology and Cardiovascular Surgery, St. Louis Park Medical Center and Hennepin County Medical Center, Minneapolis.

Other cardiologists and cardiac surgeons included in the evaluation and treatment of these patients were J. C. Dahl, M.D., B. K. Munson, M.D., L. A. Nordstrom, M.D., D. E. Raab, M.D., P. J. Ranheim, M.D., G. S. Strauss, M.D., and P. J. Wickstrom, M.D.

Supported by the St. Louis Park Medical Center Research Foundation.

Follow-up information was obtained with the assistance of the Health Services Research Center, Paul B. Batalden, M.D., Director.

The results of this study were presented at the 1979 annual refresher course of the Minnesota Academy of Family Physicians, and the Spring meeting of the Minneapolis Society of Internal Medicine, April 14, 1979.

month of surgery were contacted by phone. Follow-up information in 1978 was available on all patients. All patients who had CABS without valve replacement were included in the study, including all ages, those with poor left ventricular function (LVF), and those with aneurysmectomies. The study group consisted of 251 men (ages 29-81) and 53 women (ages 39-71), with a mean age of 55.8 years for the total group.

Patients who had CABS were classified in four arteriographic groups on the basis of the number of the three major coronary systems that had greater than 70% luminal narrowing of the dominant proximal arterial segment or greater than 50% luminal narrowing of the left main coronary artery. Patients also were classified into three groups of good, fair, or poor LVF, based on ventricular wall motion on the preoperative left ventriculogram (30 degrees left anterior oblique) and left ventricular end-diastolic pressure (LVEDP). The LVF classification is shown in Table 1. Figures 1 and 2 show examples of ventricular wall contraction tracings.

The 304 patients who had bypass surgery were divided into three groups to analyze trends over the eight-year period of the study. This separation also allowed calculation of absolute crude survival on the first 70 patients undergoing surgery before December 31, 1973. Survival of all 304 patients was calculated by the life table method.[1]

Our indications for selective coronary arteriography, coronary artery bypass surgery, and the surgical philosophy and techniques have been reported.[2] The indications for coronary arteriography, including the study of patients with atypical symptoms and repeat arteriographic studies are consistent with the recommendations of the ad hoc committee of the American Heart Association.[3]

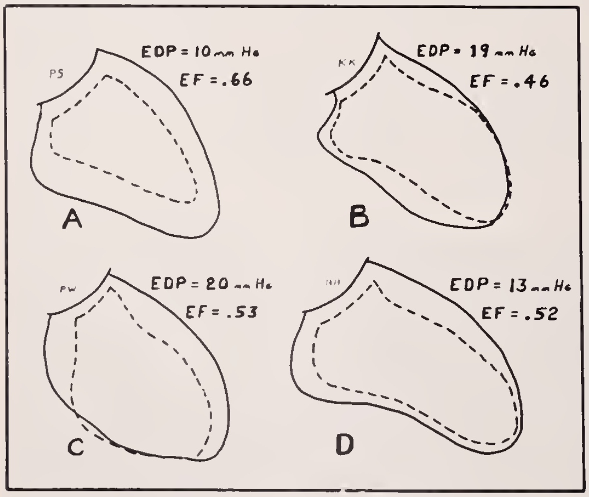

Fig. 1 — Left ventriculogram systolic and diastolic tracings (30° left anterior oblique) from patients with good (A) and fair (B,C,D) function. Solid line indicates diastole and broken line systole.

Results

Coronary Disease Profiles: 1971-1978

The profiles of the extent of coronary artery disease and ventricular dysfunction in the three consecutive groups of patients in this report are listed in Table 2. The percentage of patients with three-vessel or left main disease (mean = 63%) and the percentage of patients with ejection fractions below 0.45 (mean = 14%) remained relatively constant during the eight-year period.

Operative Mortality

The decrease in operative mortality over the eight years is shown in Table 3. This Table also shows the relationship of operative mortality to the inclusion of patients with increasingly impaired LVF. For all 304 patients, operative mortality increased progressively from 0.9% in 207 patients with normal LVF to 3.3% in all 304 patients as more patients with impaired LVF at rest are included. However, operative mortality decreased from 5.7% in the first 70 patients to 0% in the last 76 patients even though the proportion of patients with poor LVF was the same (Table 2). The improved mortality may be partly fortuitous but appears significant. Experience and perhaps better selection of patients from those with poor LVF may have contributed to the decrease in operative mortality from 1973 to 1978.

There were two deaths in the 207 patients with

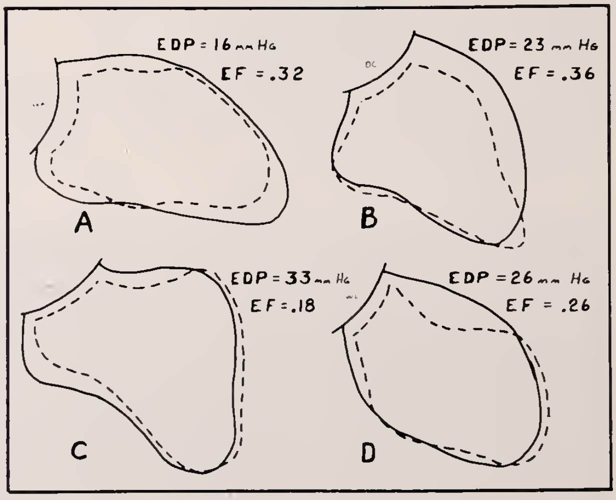

Fig. 2 — Left ventriculogram systolic and diastolic tracings from patients with poor left ventricular function. Again, the solid line indicates diastole and the broken line systole.

normal resting LVF. The first patient had CABS in 1972. He had severe distal three-vessel disease and would not likely have been accepted for surgery by current standards. He died at surgery of left ventricular failure from apparent acute myocardial necrosis.

The other operative death was in a patient with marked hypothyroidism with severe bouts of rest and nocturnal angina. Attempts were made to gradually increase thyroid replacement before surgery, but angina became worse despite propranolol therapy. Ventricular fibrillation occurred as the chest was being opened and severe pericardial abhesions inhibited attempts to manually massage the heart and promptly apply defibrillation paddles. The operation was completed successfully, but irreversible brain damage had occurred and the patient died a week later.

Table 4 divides the 304 patients into 12 groups by subdividing each coronary artery disease category into three subgroups according to LVF. Eight of the 10 operative deaths occurred in patients with three-vessel or left main disease. However, LVF was again the main determinant of operative risk as eight of the 10 deaths were in patients with abnormal (fair or poor) LVF and five of the 10 deaths were in patients with

TABLE 2

Coronary Artery Bypass Surgery
Coronary Disease Profiles: 1971-1978

Years	1971-73	1974-77	1978	1971-78
No. Patients	70	158	76	304
1 vessel disease	3%	9%	8%	8%
2 vessel disease	33%	27%	28%	29%
3 vessel disease	46%	50%	51%	49%
Left main disease	18%	14%	13%	14%
Ejection fraction <0.45	13%	13%	15%	13%
Ejection fraction <0.35	6%	2%	5%	4%
Bypass grafts/pt	2.43	2.30	2.82	2.46
Aneurysmectomy	7%	4%	1%	4%

TABLE 3

Operative Mortality (Percent)

Number of Patients	1971-73 (70)	1974-77 (158)	1978 (76)	1971-78 (304)	Total Patients
All Patients	5.7%	3.8%	0%	3.3%	304
Without aneurysmectomy	4.6%	3.3%	0%	2.7%	292
Ejection fraction >.35	4.5%	3.2%	0%	2.4%	286
Ejection fraction >.45	3.3%	2.3%	0%	1.9%	261
Ejection fraction >.55	1.9%	1.0%	0%	0.9%	207

TABLE 4

Coronary Artery Bypass Surgery — Operative and Late Deaths

Disease	Left Ventricular Function Mean Values			No. Pts.	Pre-Op Myo. Inf.	Deaths		
	Type	LVEDP (mm Hg)	EF		Percent	Operative	Late	Totals
1 Vessel	Good	12.3	.68	19	5%	0	0	0
	Fair	15.8	.54	2	50%	0	0	0
	Poor	40.5	.31	2	100%	0	0	0
2 Vessel	Good	11.3	.69	65	18%	0	0	0
	Fair	16.1	.56	12	58%	0	1	1
	Poor	20.8	.37	10	90%	1	0	1
3 Vessel	Good	9.8	.69	91	47%	2	1*	3
	Fair	16.7	.55	32	59%	1	1	2
	Poor	21.9	.35	26	88%	2	3#	5
Left Main	Good	11.5	.70	32	28%	0	1	1
	Fair	14.0	.50	8	75%	2	0	2
	Poor	18.2	.40	5	80%	2	1	3
Totals		13.3	.62	304	45%	10	8	18

LVEDP = Left ventricular end diastolic pressure
EF = Ejection fraction
*Patient died of cancer of the stomach 2 years after surgery
#1 patient died of cerebrovascular accident 6 months after erugery

poor LVF.

It is clear that in any series of patients undergoing CABS, the greater the proportion of patients with one- and two-vessel disease, the less operative risk will be involved.

Careful selection of patients can result in lower operative mortality but it is not proper to exclude all patients with poor LVF. A dyskinetic aneurysm gives a falsely poor impression of LVF by ejection fraction calculation alone. Two patients had aneurysm resections with bypass surgery because of angina and intractable ventricular arrhythmias. One patient had to be defibrillated 195 times before surgery. Both patients survived surgery satisfactorily and one was doing well four years after surgery at the time of follow-up in 1978. The other patient died of a cerebrovascular accident six months after surgery. The two patients whose ventriculogram outlines are shown in Figure 2-C and 2-D were alive in 1978, four and six years after aneurysmectomy and coronary bypass surgery.

The operative mortality in the 12 patients undergoing ventricular wall resection was 17% (two deaths), and the operative mortality in the other 27 patients with ejection fractions less than 0.45 was 11% (three deaths).

Late Postoperative Survival

Determination of long-term survival after surgery should include operative deaths and may include deaths from all causes. In this report, all deaths are included, although two of the late deaths were not related to cardiac causes.

The primary determinant of survival after hospitalization for CABS also is preoperative LVF. As Table 4 indicates, four of the eight late deaths were in patients with poor LVF. Of the 205 patients with normal preoperative resting LVF who survived surgery, two died late and one of these deaths was from cancer. The other late death was in a 65-year-old woman who had surgery in 1971 for severe angina with left main and three-vessel stenosis of the coronary arteries. She died five and one-half years after surgery and the cause could not be determined by inquiry. Thus if the noncardiac cause of death is excluded, there were no deaths within five years in the 205 patients with normal LVF who survived surgery.

Twelve of the 39 patients with poor LVF (ejection fractions below 0.45) had ejection fractions below 0.35. Five of these 12 patients died — three at the time of operation and two later.

Figure 3 displays seven-year survival calculated by the life table method for the three groups of patients

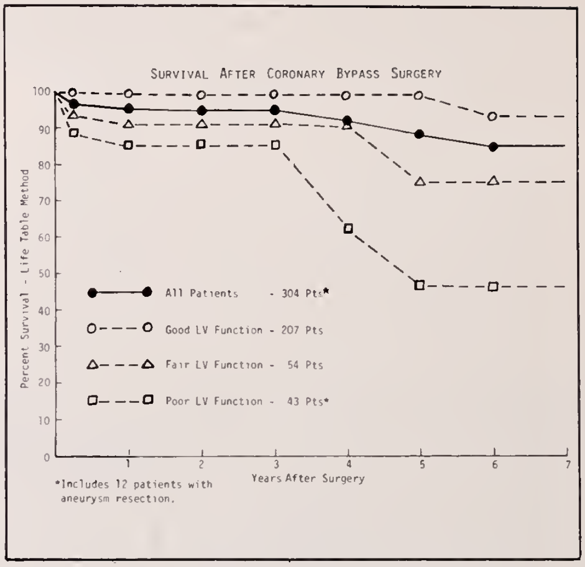

Fig. 3 — Survival after coronary bypass surgery.

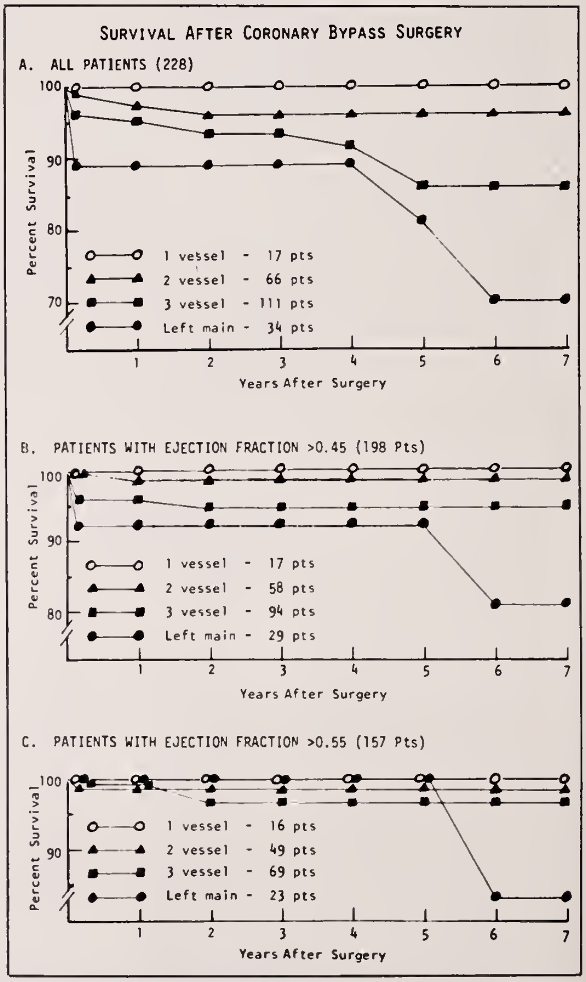

Fig. 4 — Survival after coronary bypass surgery.

with good, fair, and poor LVF. Seven-year survival for the entire 304 patients also is shown. Five-year survival for all patients was 88%.

Absolute crude five-year survival calculated for the first 70 patients who had surgery before Dec. 31, 1973, follows closely the calculated life table survival for all 304 patients. Five-year survival for the first 70 patients was 86% as compared with 88% for all 304 patients by the life table method. This difference is accounted for by the 2.4% difference in operative mortality between the first 70 patients and the entire group. If the nine patients in the first 70 patients with poor LVF (including five who had aneurysmectomies) are excluded, absolute five-year survival for the first 70 patients is 93%. Six of the 18 late deaths (two operative and four late) were from the first 22 patients who had surgery in 1971.

Figure 4 divides patients into four groups according to the extent of coronary disease and shows how survival is affected when patients with different degrees of left ventricular dysfunction are excluded. The set of survival curves for all 304 patients is shown in Figure 4A, indicating the increasingly adverse effect of the extent of coronary disease on survival. However, Figures 4B and 4C demonstrate that when patients with abnormal left ventricular function are excluded, the five-year survival is more than 90% for all coronary disease categories. This indicates that left ventricular function as an independent variable is a more important determinant of survival than the extent of coronary disease.

Five of the late deaths occurred more than three years after surgery, and four of these patients were hospitalized for congestive heart failure before death. Three of these patients had poor LVF before surgery and the other patient had fair LVF. Autopsy examinations were done in three of the patients with late deaths, and all had at least one patent bypass graft.

Impairment of LVF is most often caused by previous myocardial infarction (Table 4). Thirty-eight of the 43 patients with poor LVF (88%) had had myocardial infarction, compared with 61% of the patients with fair LVF and 31% of those with good LVF. Only 17% of the patients with one-vessel coronary disease had had infarctions, compared with 57% of those with three-vessel disease. On the other hand, almost half of the 136 patients with previous infarction still had normal LVF. This indicates that serious impairment of LVF usually is associated with infarction of myocardium supplied by more than one coronary system.

Fifteen of the 18 deaths (83%) occurred in patients with evidence of preoperative myocardial infarction. By contrast, 120 of the 286 patients (42%) who were alive had preoperative myocardial infarction.

Recurrent Angina and Graft Patency

Of the first 218 patients with one- to seven-year follow-up, 56 had recurrent angina within a year of surgery. In 49 patients the angina was significantly less severe than before surgery (Figure 5). Eleven additional patients who were initially asymptomatic after surgery had recurrent angina one and one-half to seven years after surgery. Five patients had second coronary bypass operations because of recurrent symptoms.

No apparent relationship was discerned between late mortality and recurrent angina. Only one of the patients with recurrent angina died during a mean follow-up period of 4.5 years. This patient had left main disease and died five and one-half years after triple bypass surgery in 1971. No repeat angiographic study had been done in this patient. Preoperatively, she had normal LVF. Only two of the patients with recurrent angina had poor LVF preoperatively.

In this study it was not possible to properly establish a relationship of late survival to bypass graft patency as only patients with recurrent symptoms had repeat coronary and bypass graft angiographic studies. However, it can reasonably be assumed that the patency rate of grafts studied in patients who had recurrent symptoms is less than that for patients without recurrent angina. Because of the somewhat surprising finding that none of the 51 patients who

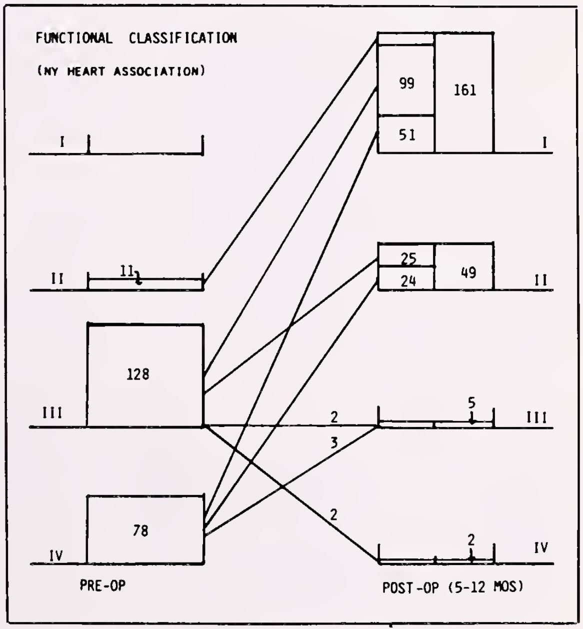

Fig. 5 — Functional classification.

were restudied died during the follow-up period that averaged almost five years, graft patency was analyzed for relationship with coronary artery pathology and changes. The 51 patients with repeat angiograms were restudied one month to seven years (mean = 18 months) after CABS.

The unexpectedly good survival in the patients with a less than ideal symptomatic result from surgery may have been related to the following findings.

1. There was a relatively high late follow-up graft patency rate (86%) in restudied coronary arteries that had progressed from partial to total occlusion after CABS (Table 5). Similar postoperative graft patency and coronary artery occlusion relationships have been reported.[4,5]
2. All patients with three-vessel or left main disease who were restudied had at least one patent bypass graft and 62% had two or more patent grafts (Table 6).
3. There was a high late graft patency rate (89%) for grafts supplying partially or totally occluded anterior descending coronary arteries. Of the major coronary arteries, the anterior descending usually supplied the largest proportion of the myocardium.
4. Only 3% of the patients with recurrent angina had poor LVF as compared with 13% for the entire study group.

Discussion

The Coronary Bypass Controversy

Since coronary bypass surgery was introduced more than a decade ago, controversy has continued about its indications and effectiveness. Those skeptical of the operation suggest that much of the apparent relief of angina is related to unphysiological factors, such as placebo effect, perioperative myocardial damage, sensory nerve interruptions, and nonspecific factors.[6–8] They point out that although some studies suggest improved survival in certain subsets of patients, those studies are marred with difficulties, and significant differences in survival are not present after two years when the numbers of patients were small. Critics also assert that if the hundreds of thousands of operations in hundreds of hospitals across the country could be examined carefully, the net effect on the natural history may be significantly adverse, especially if many operations are being done on asymptomatic patients.

On the other side of the argument, strong advocates of surgery claim that not only does the procedure provide the most effective available treatment for angina, but also it will improve survival, even in asymptomatic patients. In some centers, the emphasis has shifted from remedial to prophylactic surgery. The principle point often made is that only the anatomic changes in the coronary artery matter; whether or not the patient is symptomatic is irrelevant.[9–11] Thus, according to Selzer and Cohn, "As a consequence, coronary arteriography is being performed in many centers not as a well considered procedure in response to specific indications but as a broad means of case finding."[9]

Symptomatic Selections of Patients

Most physicians view the proper place of CABS as being somewhere between the extreme views of the controversy. Our primary indication for considering coronary bypass surgery has been the relief of angina that is unstable or unsatisfactorily controlled with

TABLE 5

Graft Patency With Recurrent Angina

Coronary Arteries, Preop and Postop	Bypass Grafts Patent	Occluded	Totals	% Patient
Total occlusion, unchanged	12	8*	20	60%
Partial occlusion, unchanged	37	22	59	63%
Partial occlusion to total occlusion	30	5	35	86%
Totals	79	35	114	69%

*Includes 4 patients with distal endarterectomies of right coronary artery and venous bypass graft

TABLE 6

Graft Patency with Recurrent Angina

Coronary Disease	No. Patients	No. of Patent Grafts 0	1	2	3	4	Total Grafts Patent
1 Vessel	5	1	4	—	—	—	4
2 Vessel	17	3	9	6	—	—	21
3 Vessel	24	0	9	10	5	—	44
Left main	5	0	2	2	—	1	10
Totals	51	4	24	18	5	1	79

medical therapy. The indications for coronary arteriography are broadened if there are marked early changes on the exercise electrocardiogram, since this finding may be indicative of severe myocardial ischemia or left main disease.[12] This approach to all patients with coronary disease is based partly on our own findings that patients with atypical symptoms, those with no symptoms or symptoms precipitated only with relatively strenuous exertion, and patients with normal electrocardiograms during and after exercise have a relatively good prognosis.[2] If there is a significant change in symptoms or in the electrocardiographic response to exercise, coronary arteriography may then be considered.

This approach to the patient with coronary disease is not without support. Selzer and Cohn[9] have emphasized two important points about what is known about coronary artery disease. First, no information at all is available regarding the prognosis of the asymptomatic patient who has arteriographically demonstrated coronary artery disease. Second, severe coronary artery disease may be demonstrated arteriographically without producing myocardial ischemia. Anatomically demonstrable lesions do not always reflect pathophysiology because of errors in interpretation caused by the unpredictable import of the length, eccentricity, irregularity, series, parallel, and collateral variations of coronary arterial anatomy.

We questioned the need to arteriographically search for coronary disease in the asymptomatic patients as early as 1971.[13] In eight years, there has been little evidence indicating a need to change this point of view.

Survival and Left Ventricular Function

Our studies have been consistent with other reports demonstrating that a major determinant of operative risk and late survival is preoperative left ventricular function. The implications of preoperative LVF have been emphasized. Ross[14] states the case as follows: "A good cardiac surgeon can select any mortality figure he wishes by selecting his patients. If patients at good risk with good ventricular function are selected for surgery, mortality figures of less than 1% can be obtained. On the other hand, if a surgeon accepts patients with a low ejection fraction and akinetic segments, the mortality will be higher. Variation in mortality is a function of the kind of patients selected for surgery as well as of surgical skill."

It is clear that patient selection is an important consideration in evaluating the results of a procedure. Survival comparisons of medical or surgical groups of patients are of little value if there are not comparable subsets with left ventricular dysfunction. The primary effort of surgery should not be to obtain the best survival by selecting only low-risk patients. With respect to survival (but not symptoms), the better the risk for surgery, the less may be the need for the procedure.[15]

This is not to minimize the importance of surgical skill, but it is important to recognize that a low surgical mortality is now expected in patients who have good left ventricular function. We currently expect a surgical mortality less than 1% in patients with good ventricular function and less than 3% in patients with mild to moderate left ventricular dysfunction.

The current difficult challenge is how to properly select the severely disabled patient with poor left ventricular function who will benefit from surgery. For the surgeon, improved techniques such as cold cardioplegia and use of the intra-aortic balloon pump may reduce surgical mortality in patients with severe left ventricular dysfunction.

Even though operative mortality is low, good surgical technique and judgment are equally important in the patient with good LVF as potential survival benefits may not be realized for five years or more. Patients with good LVF may be a good group to assess the effect of surgery on five- and ten-year survival as impaired preoperative LVF cannot be implicated in late mortality after surgery. It needs to be strongly emphasized, however, that an equally important determinant of five- to ten-year survival after surgery may be disciplined medical control of risk factors. This is one reason we like to check patients at least every two years after surgery. It may help the primary physician to have a cardiologist reinforce the importance of medical control of risk factors.

Surgery in Asymptomatic Patients

For reasons other than those already described, caution needs to be used in advising surgery for asymptomatic patients. The long-term fate of bypass grafts is not well known. If a patient with coronary disease can safely and asymptomatically live for five years before he or she is of need of bypass surgery, it would make little sense to sacrifice veins and do a thoracotomy five years before the operation is really needed.

One patient in our series was asymptomatic for seven years after CABS before he had recurrence of angina, at which time both bypass grafts had closed. He was so satisfied with the initial results of surgery he had a second operation in 1978 and has done well. He admitted that despite admonitions to the contrary, he had considered the operation curative and now is more careful about controlling risk factors.

TABLE 7

Results of Coronary Bypass Surgery

1. Significant improvement of Angina — 90%
   a) Complete relief — 70%
   b) Significant improvement — 20%
   c) Little or no change — 10%
2. Survival (overall 91% five year survival)*
   a) Good LV function — 97% 5 year survival
   b) Fair LV function — 80% 5 year survival
   c) Poor LV function — 60% 5 year survival

---

* Excluding patients with valve replacement or aneurysm resection.

TABLE 8

Indications for Selective Coronary Arteriography

A) Definite Indications
  1) Unstable angina
  2) Stable class 3-4 angina, especially with:
    a) Unsatisfactory medical control
    b) Markedly abnormal exercise ECG
B) Relative Indications
  1) Class 2 angina in young active patient
  2) Class 2 angina, especially with:
    a) Recent subendocardial infarction (esp anterior)
    b) Recent myocardial infarction in young patient
    c) Markedly abnormal exercise ECG*
    d) Planned valvular cardiac surgery in patients >40

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* Rarely in asymptomatic patient

TABLE 9

Indications for Coronary Bypass Surgery

A) Definite Indication. Symptomatic angina with good LV function and left main or 3 vessel coronary disease.
B) Relative Indications*
  1) Symptomatic angina with:
    a) Good LV function and 1 or 2 vessel disease, esp. with proximal left anterior descending disease.
    b) Poor LV function with one or more bypassable arteries, esp. if multiple vessel disease.
  2) Asymptomatic patient with:
    a) Left main stenosis, especially if severe.
    b) Cardiac valve surgery with coronary disease.

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* Indication stronger with markedly abnormal exercise ECG.

It is possible that too early or too extensive application of coronary bypass surgery may adversely affect five- and ten-year survival, even if there is less than 1% operative mortality. An inevitable minimum incidence of perioperative and postoperative myocardial infarction occurs with CABS. There is evidence that a significant amount of perioperative myocardial necrosis is related to reperfusion through patent bypass grafts rather than being related to coronary artery or graft occlusion.[16] The incidence of this complication may decrease with improved operative techniques, but any myocardial necrosis results in decreased left ventricular function.[17,18] Since left ventricular function is a major determinant of late survival, it is important to avoid any risk of premature iatrogenic myocardial infarction. None of the controlled studies give evidence that CABS reduces the incidence of myocardial infarction within three years of surgery.[17,19-20]

Summary

Our current expected results from CABS, based on this follow-up study, are listed in Table 7. Future survival may be better, especially in patients with impaired LVF, as three-year survival in patients with ejection fractions of less than 0.45 was 85% in patients who had surgery after January 1974 as compared with 67% before January 1974.

Our present indications for coronary arteriography and CABS are listed in Tables 8 and 9. We find it useful to divide indications into relative and definite categories. It is to be emphasized that patients with relative indications for surgery should be carefully selected with a greater degree of individualization than patients with definite indications for CABS.

Our indications for CABS have been gradually liberalized over the eight years of this study, mostly because continued follow-up demonstrated an acceptable and improving operative and late survival. As medical and surgical treatment capabilities change in the future, our indications also may change.

A continuing principle will be the application of what is known about the results of medical and surgical treatments to what can be determined about the patient's disease at the time of evaluation.

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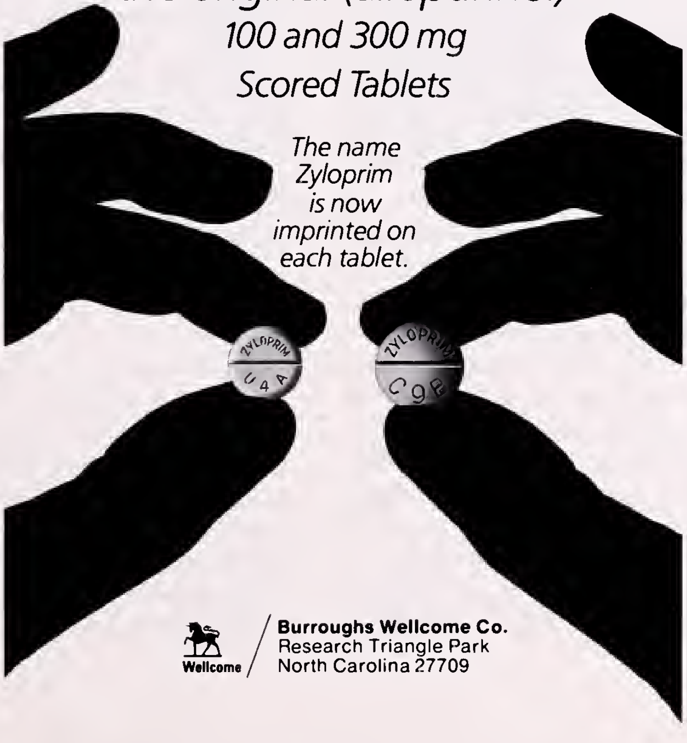

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Minneapolis Health Department

Low Birth Weight Births to Girls Enrolled in the Minneapolis Pregnant School Girl Program [*]

ELLEN ALKON, M.D.[†] AND GERTRUDE CARLSON, B.S.[†]

The Minneapolis Pregnant School Girl Program provides educational-social service and nursing help for registrants. Outcome, as assessed by percentage low birth weight, is better than would be expected from such a high risk population.

SPECIAL EDUCATIONAL programs for pregnant school girls began nineteen years ago in Minneapolis.[1] With over ten percent of 1974 Minneapolis births to mothers age eighteen and under,[2] the need for attention to this group continues (Table 1). The Minneapolis program began as homebound instruction for individual pregnant girls, then group instruction was provided, and in 1968 a comprehensive program was begun. The beginnings of the comprehensive program, which includes educational and social services from the Minneapolis Public Schools, and nursing service from the Minneapolis Health Department's Maternity and Infant Care project have been previously described.[3]

TABLE 1

Births to Teenagers in Minneapolis

	Number of Births to Mothers Age 18 and Under
1968	690
1969	653
1970	763
1971	717
1972	630
1973	586
1974	525

The comprehensive program for adolescents is called the Special Education Continuing Education Center (SECEC) and is located in a former elementary school, Holmes School, in northeast Minneapolis. It is one of the options available for pregnant school girls — the others being continuing in a regular or other alternative school program, or having homebound instruction if there is medical need, or if age sixteen — leaving school. Although there are resources available to the pregnant girl who remains in a regular school, the entire Holmes school program is tailored to the needs of the pregnant adolescent. The educational program is individualized — it can be remedial, continuing, or accelerated. The social services available are individual and group. The public health nurse is assigned full time to the program. The team approach is used — with educational, social service, and nursing staff providing an assessment of individual program needs at entry, and jointly providing service for the students. Special curriculum includes a course in child bearing and child caring which provides teaching about pregnancy and multiple aspects of parentcraft. Group counseling and education sessions with the social work and nursing staff meet weekly. Transportation is provided by school buses from any site within Minneapolis. Food service at the school includes breakfast, lunch and afternoon snack. Simple modification from the regular school meal package such as providing additional milk and other nutritious foods allows it to meet the needs of pregnant adolescents. The physical education program is daily prenatal exercises. Planning for continued service after the girl returns to her home school includes communication with the home school, continued public health nursing service, and the availability of school-based day care. Tracking through the school census allows some continuing assessment of the educational achievement of girls who have attended Holmes School.

Since diagnosis of pregnancy is a prerequisite to entry to the program, most students have initiated prenatal care. The public health nurse provides encouragement for continuing prenatal care, communicates as needed with the care source, interprets special health needs to school personnel, provides individual and group health counseling and teaching, makes indicated referrals such as to the public health nursing for home visiting, does family planning

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[*] Presented, in modified form, to the Northwestern Pediatric Society, September 17, 1976.

education and counseling, and provides school staff with consultation regarding the health program. She is a staff member of the maternity and infant care project, is supervised by the maternal and child health nursing coordinator, and has the back-up resources of the health department. Although a maternity and infant care project maternity clinic was located in the school for seven years, it was moved to a larger location before the last school year. Holmes school girls generally use other sources of care, with over 90 percent reporting care sources other than the MIC project.[4]

Although there are other educational options available for pregnant school girls, and there is increasing local acceptance of the pregnant school girl in her home school, there is continued substantial enrollment in the program for pregnant school girls (Table 2). Approximately 23% of girls under age 19 giving birth in Minneapolis have registered into the Holmes school program in the past seven years.

TABLE 2

Enrollment in the Educational Program for Pregnant Girls Minneapolis, Minnesota*

School Year	Number Students	Approximate Non-Resident
1957 (Homebound)	35	
1961-62 (N.E. Neighborhood House)	42	
1962-63	70	
1963-64	103	
1964-65	125	
1965-66	120	
1966-67	161	25%
1967-68	170	38%
1966-69 (Holmes School)	198	37%
1969-70	228	25%
1970-71	208	25%
1971-72	211	24%
1972-73	166	23%
1973-74	171	22%
1974-75	184	16%
1975-76	175	10%

*Source SECEC Statistics

Profile of Students in the Program

School statistics obtained at enrollment show a high proportion of young, unmarried, and minority students and suggest a high proportion of students from lower income families. Over one-third are under age 16, over one-third are minority, and 88 percent are unmarried. Among the 67% of enrollees reporting income in 1974-75, 81.5% reported a total family income of $5,999 or below. Holmes student reports on their living arrangements during 1972-73 through 1974-75 suggested broken homes. Only 25.1% were living with both parents and 5.5% with a husband only (half of the married students).[5]

Reports to the nurse revealed a high proportion of students who delivered in the Holmes program reported cigarette use during pregnancy and previous experience with drugs. Over 50% of the students reported smoking during pregnancy. One-fourth of the smokers smoked one pack a day or more. Although students did not report drug addiction, 44% reported illicit drug use although for 25% of the students the only drug reported was marijuana. The high proportion of drug experimentation suggests that drug addiction may have been present in some. One index of the social or emotional turmoil of these girls is their reports of suicide attempts. There were reports of previous suicide attempts in nearly 6% of the students.

Educational follow-up of Minneapolis registrants in the program for pregnant school girls showed that slightly over half of those with known status either graduated from high school or were continuing in school one year after the year they were enrolled in the program. The educational outcome for seniors enrolled in the program was better: 76.3% of the seniors enrolled in 1972-73 graduated as expected.[5]

Study of Infant Outcome

Since the maternity and infant care project has provided a nurse to the program for eight years, it was decided to look more closely at infant outcomes as an index of the impact of the program. Evaluation of comprehensive programs for pregnant school girls is difficult because of the relatively small numbers of girls involved, the lack of a true control group, and the multiplicity of factors which impinge on outcome. Methodologic problems have been discussed in the literature,[6,7,8] yet there have been reports of maternal and infant outcome from pregnant school girl programs which suggest improved outcomes.[9,1011]

Methodology

Nursing records, both individual and student nursing records, and lists prepared by the nurse formed the basic material analyzed. The nursing record includes part of the school information, a nursing interview, and follow-up notes made by the nurse. Complete nursing records were available from 1972-1973 on, or for the past four years. The outcome factor selected was low birth weight, as this might be expected to be influenced by a comprehensive program, and has often been selected in similar program analysis. The Holmes school outcomes for September 1972 to July 1976 were compared with all

Minneapolis resident births for 1973 (the last year for which information on low birth weight births to teens is available). Since the impact of the program was the focus of the study, it was decided to eliminate all instances where the students were registered into the program for less than one month, where outcome was not known, and where the student had withdrawn from the program more than a month before delivery as the effects of the comprehensive program might not bridge that time. Students over age 18 at the time of delivery were also eliminated as they were not high school age.

Results

Using the above criteria there were 359 students, 284 Minneapolis residents and 75 non-residents. This is 68% of enrolled students. The resident and non-resident students were similar in age and previous obstetric experience. Nearly one-third of both groups were under 16, and 94-95% were primigravidas. The non-residents however had a smaller proportion of minority and married students, as they were 93% white and 96% unmarried. The low birth weight percentage among non-residents was 5.4%. Only the outcome of resident students was compared to Minneapolis outcomes. Figure 1 shows birth weight outcome for Minneapolis resident students and for teen births in Minneapolis. Although the 7.0% low birth weight percentage for the Holmes school girls births is below the 8.4% low birth weight of Minneapolis teens in 1973, there is not a significant difference between these groups. The Holmes school group however is a higher risk group with a high proportion of young, minorities, and unmarried teens. Figure 2 shows that Holmes school had twice the proportion of girls under 17 as the city, yet similar outcomes. The low birth weight percentage among those 16 and under in 1973 was 4.8% compared to 6% among the Holmes school residents. Minneapolis in 1973 showed favorable pregnancy outcomes for young teens.

Figure 3 shows that Holmes school had a higher proportion of minorities than the total city, and within most groups had lower percentage of low birth weight infants. Black resident students constituted 32.4% of the Holmes school group, and had a low birth weight percentage of 8.7% compared to the city-wide percentage of 12.9%.

Figure 4 shows the higher proportion of unmarried mothers from Holmes compared to the city's teenage parents, and lower low birth weight percentages for both married and unmarried than in the total city. Among unmarried students there were 7.4% low birth weight births compared to 8.5% low birth weight

Outcome of Pregnancy for Mothers in SECEC School Year, 1972-1975 Compared to All Minneapolis Births to Mothers Under 19, 1973

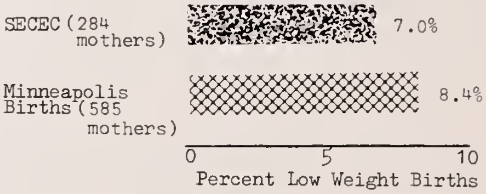

Figure 1

Outcome of Pregnancy for Mothers in SECEC Compared to All Minneapolis Births, By Age

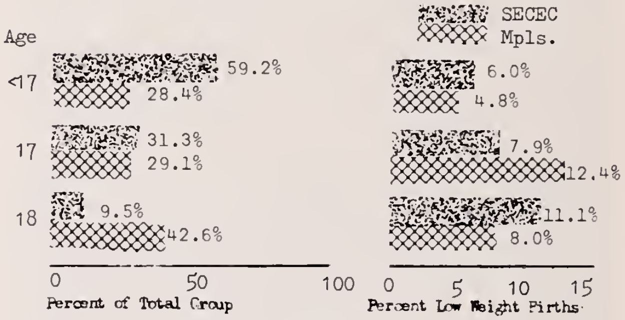

Figure 2

Outcome of Pregnancy for Mothers in SECEC Compared to All Minneapolis Births, Mothers Under 19, By Race

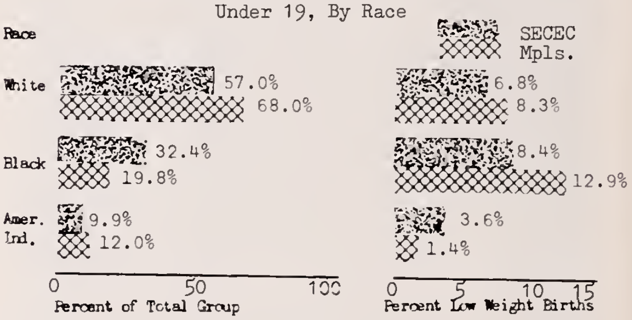

Figure 3

Outcome of Pregnancy for Mothers in SECEC Compared to All Minneapolis Births, Mothers Under 19, By Marital Status

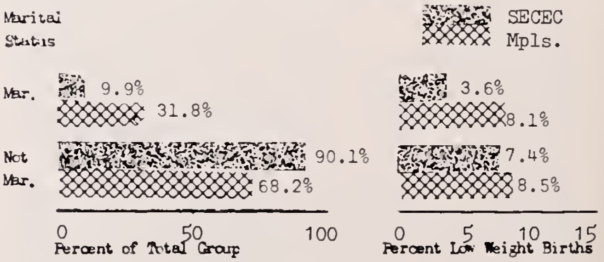

Figure 4

among Minneapolis unmarried teens.

Discussion

The Holmes school population shows demographic characteristics which have been associated with less favorable pregnancy outcome. These characteristics include young maternal age, high proportion of minority mothers, poverty, and illegitimacy.[12,13,14,15,16,17,18,19,20] The student profile also shows over half of the students smoke cigarettes, and 44% have used illegal drugs: both smoking and drug abuse are associated with low birth weight.[13,21] The analysis above suggests higher obstetric risk at Holmes than among the rest of Minneapolis teenage parents, the low birth weight percentage is not increased, but indeed lower than that of the city, suggesting that the comprehensive program may have been of benefit.

Conclusion

The comprehensive program for pregnant school girls in Minneapolis has provided full time multidisciplinary educational-social service-nursing help for pregnant school girls for the past eight years. The girls served by this program are younger, more likely to be minority, and less likely to be married than the total teenage mothers in Minneapolis. Despite their greater risk, the low birth weight percentage is not increased over that of total teenage residents.

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HEW Announces Appointment of Dr. Robert Kelly to the National Professional Standards Review Council

Dr. Robert T. Kelly of Grand Rapids, Minnesota has been reappointed by former HEW Secretary Joseph A. Califano, Jr. to the National Professional Standards Review Council. Dr. Kelly was sworn in on September 10th by Leonard D. Schaeffer, Administrator of the Health Care Financing Administration. Dr. Kelly has served on the council since 1976, and his appointment is for a second term. Dr. Kelly currently serves as the chairman of the American Medical Association Council on Medical Service.

Rural Physician Associate Program

RPAP — A Boon to Rural Minnesota

JAMES K. HEID, MD*

Inner city and rural areas have long faced serious difficulties in delivering adequate health care. Minnesota's Rural Physician Associate Program may provide a key toward solving the rural half of this problem.

"You can take the boy out of the country. . ." but once the boy becomes a doctor how do you get him back there again?

Such was the question posed by the Department of Family Practice and Community Health at the University of Minnesota. Their answer: RPAP, the Rural Physician Associate Program. This program boldly uproots the third year medical student from the structured academic setting and plants him into the free style practice of a rural physician. The student works with the rural doctor for twelve months and receives a $10,000 stipend. The state provides $5000 of this, tax free. The remainder is paid by the physician preceptor. The student earns two quarters of academic credit for this year in the country. RPAP aims at two major goals: (1) furthering the medical education of the student through close association with seasoned clinicians; and, (2) exposing students to the attractions of life and practice in rural Minnesota.

The Rural Physician Associate Program annually places forty students in small outstate communities. The plan has been in operation about seven years. So — how is it working? Is RPAP helping the student? Do rural physicians favor the program? Has the rural community benefitted?

In a central Minnesota community of 8000 our four-man group of family doctors† has logged five years experience with RPAP. Five students have thus far survived this particular exposure. This report tells of our impressions and our experience with the program. It is the viewpoint of a rural family physician.

RPAP and the Medical Student

What better way for a student to test an interest in rural medical practice than a system of total immersion? And total immersion is what RPAP is all about — immersion into the preceptor's full spectrum of professional and community involvement. During the first few days the student may literally shadow the steps of his preceptor. One day's exposure could run from rheumatism, Rotarians and rashes to golf, gallstones and gout. Students blend into community life with surprising ease. They speak at the hospital, at schools, and at service clubs. They assist at public health screening programs and immunization clinics. They join the Jaycees and church youth groups. In a short time their community acceptance is solid and sincere.

It is no surprise to learn that the third-year medical student is bright, eager and well-founded in basic medical theory. The surprise, and it comes each year, is to learn that the student is elegantly green in clinical experience. Generally he has never started an IV, sutured a wound, applied a cast, or done a proctoscopy. Thus the first weeks with each student demand a slow painstaking review of clinical procedures. This takes time and dictates harsh pruning of the preceptor's appointment schedule. Fortunately, rural family practice superabounds in clinical contacts and students learn fast.

The student is introduced as a "student doctor" and patients are aware of his true preceptorship status. Yet, for perhaps the first time in his career, the student is not only greeted as "doctor", he is respected as one. Few joys can match the silent pride of a student as he walks into a cafe and hears a small toddler call out "There's my doctor".[1] Treated with professional dignity and given responsibility commensurate with increasing skills, the student gains confidence, blossoms and thrives.

Still the University does not abandon the student to the wiles of the boondocks. Once a month a University faculty member visits the student. He acts as a consultant for rounds, outpatient problems, and for a formal teaching presentation conducted by the student. Hospital staff physicians and paramedical personnel are welcomed to these teaching programs. Twice a year communication experts come to the community, video-tape the student as he interviews a patient, and assist him in strengthening communication skills. University sponsored seminars in marriage and family problems are held for the students quarterly.

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*Little Falls, Minnesota

†Little Falls Medical Center, RA Stoy, MD; S W Watson, MD; HA Scanlon, MD and JK Heid, MD

By the time the year is completed the student has gained significant clinical experience. He has delivered 25 to 50 babies. He has repaired countless lacerations. He has reduced several Colle's fractures and other fractures, and he has first assisted at a wide range of surgical procedures. He has done venous cut-downs, spinal taps, and tracheal intubations. He has managed a large variety of medical problems and has achieved fair competence in handling critical care and coronary care patients. He has also observed the need in private practice for deft business and management skills. In one year the student develops surprising professional maturity. In the classroom of real life he has learned that sound medical practice is born of sound medical theory. He has seen how rural family practice can bend or break a man but how it rarely bores him. He has witnessed the challenging clinical mix of the mundane and the monstrous. And he returns to academia a wiser, more confident, more searching student.

RPAP and the Rural Physician

It was a discovery made late — a discovery of the obvious. The doctor discovered that teaching is a most underrated challenge. For twenty years he had done tonsillectomies in his own style and technique. In time he had developed a systematic approach to diagnostic problems. Over the years his entire practice had become honed, shaped and patterned. Suddenly the peace was shattered by a brainy young student with a dogging persisting question; "Why?" Why indeed! How does one explain the professional habits and pretensions of a lifetime? It is mind-boggling! The transition from practitioner to teacher terrifies and humbles. It frustrates and positively defies endurance — except that it is so wonderfully stimulating. It stimulates and revives scholastic interests long lulled into dormancy. Yes, teaching is an awesome art! To teach is to learn, and in the end the teacher always learns more than the student.

RPAP builds bridges of good-will between the University and rural doctors. Many physicians recall the days when the hapless and hopeless referring LMD was dismissed with scorn at the professor's grand rounds. Times have changed! Monthly University faculty visits have done much to dispel the doubts. When men of the professional stature of Dr. John Najarian, Chief of Surgery at the University, come out to the rural hospital, make rounds, break bread, and discuss common problems with the local medical staff, new bonds of understanding grow quickly between small town and gown.

Faculty visits afford excellent educational opportunities to local medical and paramedical personnel. These visits often bring super specialists into areas that have seldom known this expertise. Between student queries and faculty discourses, RPAP offers, and prods, the rural physician into an extended program of continuing medical education.

The prestige of an appointment to the clinical faculty of the University was seldom available to the rural doctor of the past. With the coming of RPAP, rural physicians contribute hundreds of volunteer teaching hours to medical students. This often leads to an appointment as "Clinical Assistant Professor" in the department of Family Practice and Community Health. A satisfying recognition, and as one friend commented, "Not bad for a country bumpkin".

The rural physician today is something of a breed apart. He thinks he owns the best of both worlds. He lives and works in a rustic, often pastoral, setting. Still, with the ease of modern transportation, he finds that the cultural and recreational attractions of the city lie within his easy reach. Granted, it was not always so. The beloved horse and buggy doctor of the past suffered professional isolation and grueling demands on his time. It may even be this persisting image of loneliness and fatigue that accounts in part for the rural doctor shortage today. False images die hard. RPAP places the student in the country to find out for himself.

Each student rightly brings a bag full of questions about the rural area: Is the air clean and the water pure? Are the schools educationally sound? Does rural group practice provide free time for fun and family? Are people friendly? Is the crime rate low? Is the pace of living slower? Are there fish still to be caught? Are golf courses less crowded? Are family bonds closer and marriages more stable? Is the quality of life really that good? To all these questions, the rural doctor promptly answers, "Yes, we think so". But perhaps the lakes and streams, the woodlands and open spaces have cast their spell upon us!

RPAP and the Rural Community

Throughout this essay the medical student has been portrayed as a male. No sexist slur was intended, only grammatical grooming. In point of fact, one of our students was a personable young woman. As best we could determine, she was the first female 'physician' to practice in our area. Initially we thought this might be a source of concern. No problems! She handled it with poise and charm. Men rarely objected to consulting her and women often preferred her to their regular male physician. She was in demand as a speaker. Best of all, she visibly demonstrated to school girls that the professional life was indeed open and accessible to women. And she barely blushed when a brusque young farmer bellowed across the ballroom "So dis is da *woman* doctor". No question about it, this student was very good for our community. But all medical students are good for a community. They bring a certain freshness and intellectual spark that is subtly contagious.

Does RPAP motivate the student to later return to the rural area as a fully trained doctor? This, of course, is the ultimate test of the success of the program. Seven years is really insufficient time to make a meaningful judgment, but Dr. John Verby, a prime mover of the program, reports that at least twenty-one RPAP students had settled in rural Minnesota by 1976.[2] In our own case, our first RPAP student returned to join us in practice. And it may signal the wave of the future to note that this young physician, an honor student (Phi Beta Kappa and Alpha Omega Alpha), chose primary care rather than academic medicine or research. RPAP could just become the best doctor recruitment program that the rural areas have known.

Conclusion

Quietly but decisively in the past seven years a new program in medical education has gently sprinkled its blessings on rural Minnesota. It provides sound education for students, it gives new inspiration to rural doctors, and it offers great promise of recruiting more physicians for rural communities.

In the Rural Physician Associate Program, the University and the State legislature have collaborated on a program that may well rejuvenate rural health care. They deserve high praise, thanks, and support. Indeed, it is this type of effort that helps produce and preserve the good life in Minnesota.

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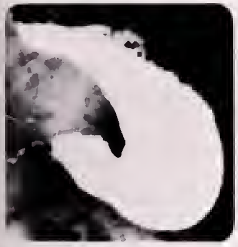
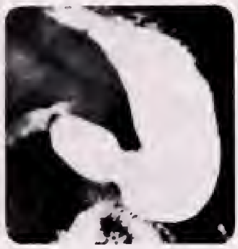


Pylorospasm has almost totally blocked passage of barium meal.



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*This drug has been classified "probably" effective in treating functional bowel/irritable bowel syndrome.

†See Warnings, Precautions and Adverse Reactions.

See following page for prescribing information.

Reference:
King, J.C. and Starkman, N.M.: Evaluation of an antispasmodic. Double-blind evaluation to control gastrointestinal spasms occurring during radiographic examination. A preliminary report. Western Med. 5:356-358, 1964.

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Final classification of the less-than-effective indications requires further investigation.

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Do not rely on the use of the drug in the presence of complication of biliary tract disease. Investigate any tachycardia before giving anticholinergic (atropine-like) drugs since they may increase the heart rate. With overdosage, a curare-like action may occur. ADVERSE REACTIONS Anticholinergics/antispasmodics produce certain effects which may be physiologic or toxic depending upon the individual patient's response. The physician must delineate these Adverse reactions may include xerostomia, urinary hesitancy and retention; blurred vision and tachycardia, palpitations; mydriasis, cycloplegia; increased ocular tension; loss of taste; headache, nervousness, drowsiness; weakness, dizziness; insomnia, nausea, vomiting; impotence, suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestations; some degree of mental confusion and/or excitement, especially in elderly persons; and decreased sweating With the injectable form there may be a temporary sensation of lightheadedness and occasionally local irritation. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual patient's needs

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Product Information as of October, 1978.

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Pediatrics

Television and Children

A Physician's Guide

ROBERT DEVNEY M.D. * and ROBERT W. ten BENSEL M.D.†

Television is present in 98% of American homes. It is watched by almost everyone with an average peak viewing time in four and five year olds of 60% of their non-sleeping hours (54 hours per week). More TV is watched for the first eighteen years of a child's life than any other activity save sleep.

TV has several health hazards. It has been shown to significantly displace several activities including exercise, play or other extracurricular activities in some children. It fosters poor health habits, and it causes an increase in the acceptance of violence. Developmental reasons regarding TV's differential effect on children from adults are discussed.

Several suggestions about what parents and physicians can do about controlling this potential health hazard in children are given.

TELEVISION CAN be found in 98% of all American homes, more homes than have adequate heating or plumbing.[1] Children in our society spend more time watching television than any other activity save sleeping. Typically children watch TV about three hours a day, seven days a week; or by the time a child graduates from high school he/she will watch 15,000 hours of television. This is compared with 11,000 hours of classroom instruction received during the same period.

What makes TV so different from the other media? One of its qualities is that it produces a trance-like state in the viewer.[2] Perhaps this is due to its ability to remove all active participation from its viewers. The viewer need not fantasize; he/she can just sit passively in front of the set devoid of creative activity. Another reason for TV's effect on the American family is its ready availability. Television is ubiquitous and is free after the initial purchase. Television is often used as an electronic babysitter. In fact, 80% of U.S. parents use television in this way.[1] More important is that parents seldom know what their children watch on TV, let alone control what is watched.

Over the last 25 years 2,300 studies and articles have been written on TV's effects on children.[9] Most of the results of these studies have demonstrated the predominance of negative influences TV has on children. What are some of those influences this electronic form of mass media has on the growth and development of children? Several factors delineated in Table 1 are the topics of discussion of this article.

TABLE 1

Some General Comparative Aspects of Television

Positive Aspects of Television	Negative Aspects of Television
—TV increases the knowledge of the world about us albeit somewhat superficially. —TV is a constant source of new vocabulary. —TV has the potential of increasing our understanding of other peoples and cultures and other ways of thinking. —There are a few TV programs directly aimed at children which use a pro-social model of behavior.	—TV decreases school performance. —TV displaces many non-school activities from a child's life including creative play, physical activities, family interactions and reading. —TV causes a greater acceptance of violence. —TV gives poor nutritional advice to children. —TV has a tendency through its commercials to foster a consumer "buy, buy, buy" orientation among its viewers. —TV presents racial, sexual, ethnic and religious stereotypes as its dramatic characters. —TV has a tendency to present only one dominant view of our world situations and human interactions, thus melting away our cultural plurality and replacing it with its own dominant sensational view of events.

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Time

The television is turned on six hours and 18 minutes per day in the average American home.[3] It is part of the background of American life, always there and very much a part of the family. Pre-school children now watch on the average of about 23 hours of TV per week.[4] But if one takes just four and five year olds the average viewing time is 54 hours per week.[5] This translates into about 60% of a child's non-sleeping life.[6] For grade school children this seven and a half hours per day decreases to about two to three hours, but more than one-third of these children watch double this amount.[7] By the time a child is seventeen he/she watches "only" two hours and 20 minutes a day.[5]

Television has altered the pattern of our lives. "By the mid-1960s 55% of American families had changed their sleeping habits for TV, 55% had altered their mealtimes, and 78% had begun to use television as an 'electronic babysitter.' Visiting others and entertaining at home also have reportedly decreased and the use of other media such as radio and movies has been adversely affected. Other activities such as reading, creative leisure activities (e.g., correspondence and knitting) and household cares are also decreased because of TV."[3]

What effect does the actual viewing of TV have on children? After one hour of TV viewing exhaustion sets in for children up to the age of five or six years.[8] This exhaustion can prevent children from carrying out regular exercise vital to their health. Researchers have noticed a decrease in creative play associated with TV viewing. TV fosters the attitude of spectatorship in children and it teaches passivity of cognition and human interaction.[9] With the exception of verbal skills (increased with TV viewing but without a concomitant increase in verbal comprehension) TV viewing can actually be a detriment to school performance.[9] This is particularly true when the TV viewing is heavy enough to displace creative play, physical activity, parental interaction or reading.

Violence

Violence is part of today's television. It is part of almost every TV show. By the time a child is eighteen years old he/she will see approximately 18,000 murders.[9] That eighteen-year-old will also have seen countless assaults, rapings, muggings, and cases of arson on TV. However, probably more important is the fact that the child sees violence as a role model for resolution of interpersonal conflicts.

Overt violence exists in about 80% of the television shows most often watched by children (prime time and Saturday mornings).[3] On Saturday mornings, the TV fare made expressly for children, overt acts of violence occur on the average of more than one per minute.[9]

The TV industry in a compromise move to assuage the avalanche of public opinion came out in 1975 with the family hour. The major problem with this action is that it is grossly inadequate. Many children watch TV beyond the prescribed family hour boundaries. "More than 20 million children, two to 17 years, are still watching at nine p.m., 13 million at 10 p.m., and 5.3 million at 11 p.m."[5]

The premier question still is, "does TV violence help cause violence?" This is a most important question because our society is a violent one, particularly with regards to our youth. Since television began violence to and by youth and children has sky-rocketed. Suicides have doubled in incidence from 1950 to 1973. Murder has doubled in incidence from 1960 to 1974. The incidence of murder in the U.S.A. is ten times that of the Scandanavian countries.[5] Television as a parallel during the period of the late fifties and sixties has gone from being non-existent and non-violent to having an essentially violent format and being very much a part of American life. In 1954 approximately 17% of TV shows were essentially of a violent nature. This figure rose steadily until it hit 80% in the middle 60s and has changed little since. TV violence and violence in American life have risen together over the last 15 years. American life is complicated and the causes of human behavior are complex. However, TV is a powerful medium or in the words of Joseph Morgenstern:

> "It's not enough to say that Shakespeare and Marlowe were violent and civilization still survived. Technology has brought a new amplification effect into play. Never before has so much violence been shown so graphically to so many."[10]

Most studies on TV violence and its effect on children are short range studies. Several studies have demonstrated that when children viewed violence-filled programs they were much more likely to be more aggressive, to have a decreased sensitivity to real violence and to demonstrate non-cooperative behavior.[3] These studies used several different settings, different methods of measurement and different scales of measurement. The results were all the same: violent TV causes violent children. The more violent the TV (both quantity and quality) the more violent the child. Young children were more affected by violence (in terms of patterning of behavior) than were older children.[3]

There are fewer studies on the long-term effects of violent TV on children. Bandura (1965) demonstrated children can copy novel aggressive actions up to six to eight months later.[3] Eron et al. in 1972 concluded a study which began ten years earlier. They initially took 400 boys aged nine years and measured aggression (both self and peer reporting), socioeconomic backgrounds and TV viewing practices. Ten years later their aggressive behavior was measured. The best predictor of the level of the nineteen year old's aggression was the amount of violent TV viewing at nine years (Figure 1).[3] One researcher put it this way:

> ''If you believe there's a link between cigarette smoking and cancer, then you probably ought to believe there's a link between watching TV violence and human aggression.''[11]

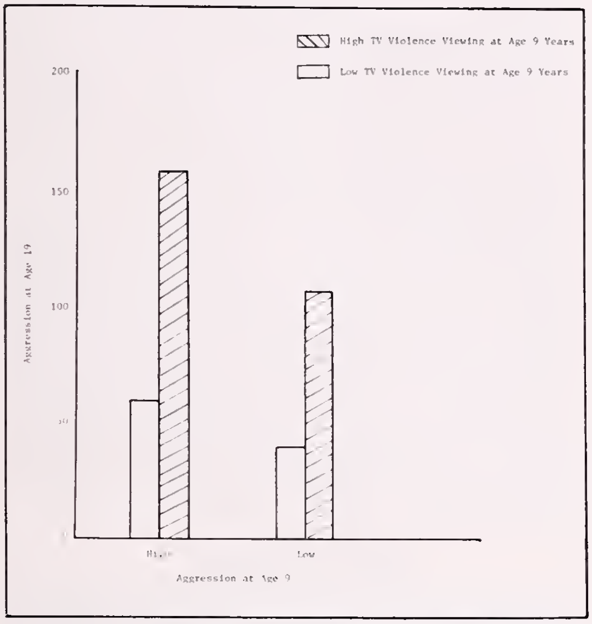

Fig. 1—Mean Aggression Scores for Boys Age 19.[3]

Health

As health promoters and care givers, we should be especially sensitive to the messages TV gives to children concerning health, and we should be interested in what effect these messages have on kids' behavior. TV's main influence on children and their health is through its influence on drug use/abuse and on children's diet. Most of TV's influence in this area comes through its commercials. Drug commercials are not aimed at children. However, by the time a child reaches 18 years he/she will have watched approximately 350,000 commercials[9] of which many advertize over-the-counter medications. Generally children believe these commercials at face value. In fact in one study 70% of fifth and sixth graders believed the messages drug commercials were giving them, even though 70% of the information given had been determined to be inaccurate or misleading.[8] This does not imply drug abuse, however as Peterson et al. state in their study on the effect of TV drug advertisements:

> ''Our findings do not establish a causal link between drug advertising and drug abuse. However, they suggest that drug promotion on TV tends to encourage favorable attitudes towards drug use through exaggerated claims and through failure to point out the need to exercise appropriate caution in drug taking. Other studies have implied a relation between the susceptibility of drug-using individuals to advertising and their tendencies toward drug abuse. Considering these factors, the prevalence of drug advertising and the big degree of credibility TV has among viewers, we must conclude that ads should be assumed to influence the public toward heavier use of drugs unless proved otherwise.''[12]

Seventy-eight percent of Saturday morning commercials (those aimed directly at children) advertise either sugared breakfast cereal or snacks. These figures would be of little concern if these products did not become part of the viewer's diet. Several studies have shown that children frequently ask their parents for such food products and that their parents buy these products for them, thus incorporating these advertisied candied products into their diets.[13] Or as one report puts it, ''This (TV) is the most massive educational program to eat junk food in history . . . we are creating a nation of sugar junkies.''[2]

Learning and Development

What is the difference between how a child watches TV and how an adult does? However inane or simplistic TV drama may seem to the adult, it is exceedingly complex to the child. The action of one scene which is very obviously related to the action of the next in the eyes of the adult may not at all be connected in the child's eyes. There are many factors involved in these differences.

One of the major factors in understanding a TV drama is the viewer's ability to remember the essential facts of the story. Collins demonstrated that second grade children recalled only 66% of the scenes which adults deemed essential to the plot of an hour long action adventure. This is opposed to an 84% recall of the scenes by fifth graders and a 92% recall by eighth graders. Additionally, second graders tended to have an increased report of non-essential scenes and information as compared with other ages.[14] Therefore as the child grows older there seems to be an increased ability to remember essential scenes and filter out extraneous information.

How well do children understand the cause-effect nature of a particular TV program or a particular TV character's behavior? Collins in another study presented a violent TV program to kindergartners, to second, fifth and eighth graders. He then measured their memory for plot and their understanding of the characters' motives and consequences of their actions (Figure 2). Kindergartners generally remembered only the aggressive actions. Second graders remembered either only the aggressive acts or the aggression and its consequences but no motives. But by the time the children were in eighth grade they had a relatively clear understanding of the motives of aggression.[15] In another study Collins and his associates took a group of children and showed them a TV program, half of which they projected a TV show in its normal chronological order and half of which they completely scrambled the scenes. The second graders reported no differences in response between the two shows, but the adolescents were greatly confused by the lack of temporal relationships in the plot.[14]

In addition to a decrease in memory and cognitive skills, children also process TV differently from adults for other reasons. Children 11 years or older generally have a good separation of their fantasy life from other aspects of their life. This certainly is not true with preschool children and is relatively not true with early grade school children.[15] TV programming is considered more of a reality to younger children than to older ones.

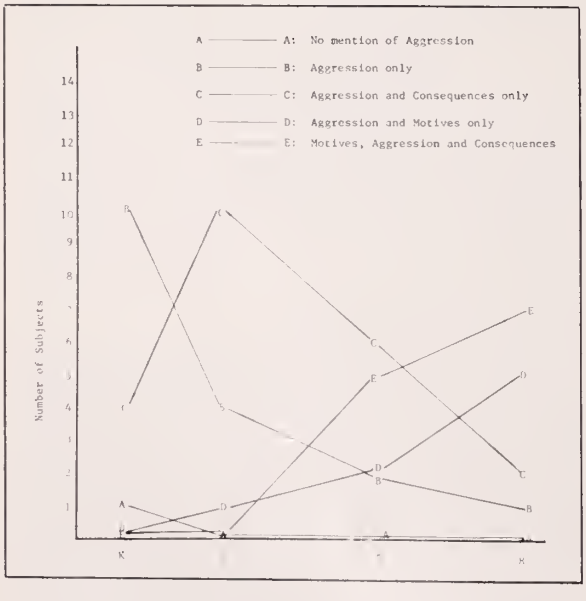

Fig. 2—Age Trends in Comprehension of Motives and Consequences Cues in Relation to Aggression.[15]

Younger children also have less experience (of "internalized social knowledge") for contrasting human interactions with TV human interactions.[15] Therefore, younger children are not able to determine very easily what is "appropriate" on TV and what is "nonsense". Younger children do not have their parental/societal values for purposes of contrasting with TV.[15]

Therefore, (1) children have less ability to remember the essential scenes and facts subsequently leading to a tendency to select out dramatic action-packed scenes of a program; (2) they have less ability to follow a plot line and understand motives and consequences of dramatic scenes; (3) they have less social knowledge and social values upon which to evaluate these scenes; (4) and they have less ability to realize that the dramatic scenes on TV are fantasy and not really part of real human interactions. Therefore, children develop TV interactions as role models. TV does raise our children, and raise them to a more profound degree than most of us realize.

For most children TV will have little effect on them unless the amount of time and violence watched overwhelms the child, then severe problems can occur. If there is parental neglect (lack of parent-child interaction), there is trouble. If you belong to a population sub-group which is significantly stereotyped on TV (which is just about everybody), you may have trouble. If you are poor, you have trouble. If you are a child with nothing going for you and nothing to do, you are in trouble.[2]

Recommendations

Using TV as a baby sitter and denying the child normal parent-child relationships could be considered a form of "child neglect", but almost all of us do it. How many parents interact with their children while their children are watching TV (NOT just watch TV with them)? How many parents set limits on how much TV can be watched or how much violence can be watched (if any)? How many parents actively select and review their child's TV programs? Yet there are the types of actions that must be taken by parents for the well-being of their children.

Many parents feel that the best solution is no TV at all. Since almost every house has a TV, it is just as easy for children to go over to the neighbors for television. This is especially true if the child perceives no TV viewing as an unreasonable request.

Many parents come up with other formulations such as no TV before or after supper or no Saturday morning TV. Often this is tempered with exceptions for special shows of unusually high quality. Firm rules for children are difficult to enforce if children see their parents breaking the rules for no apparent rational reason. Children will usually understand a consistent logical explanation. This is so even if it differentiates between children and adult privileges if the child's welfare is truly kept in mind and is not at direct odds with parental behavior.

As a physician what can be done? San Francisco's Committee on Children's TV, Inc. (1511 Masonic Avenue, San Francisco, California 94117), a non-profit heterogeneous group, set up a series of questions, "General Guidelines for Selecting TV Programming for Children," for the evaluation of TV content (Table 2).[9] These guidelines can be given to parents. Many parents have no idea of the power of TV and as doctors (educators) we have the responsibility to make this public health problem known. Particulars can easily be discussed with interested parents concerning the effects of increased viewing, violence, health hazards and developmental effects of TV. Being aware by just asking, "What is your favorite TV program?" is probably not enough, but it is a good foot in the door. An adequate history should probably include the amount of TV watched and what types of shows are watched. More important is whether parents play an active role in their child's TV viewing.

As a concerned citizen many things can be done. The most concerted effort is being put out by the Parents-Teachers Organization. They along with the medical profession are the most active in the field. The PTA is developing a grassroots campaign, primarily concerned with TV violence, trying to influence the industry to present programming alternatives to violence saturated TV. Local PTA representatives can easily be contacted for further suggestions.

TABLE 2

General Guidelines for Selecting TV Programming for Children

1. **Does the program appeal to the audience intended?**
2. **Does the program present racial groups positively and does it show them in situations that enhance The Third World Child's self-image?**
3. **Does the program present gender roles and adult roles positively?**
4. **Does the program present social issues that are appropriate for the child viewer and perhaps are something a child can act on at a child's level?**
5. **Does the program encourage worthwhile ideals, values and beliefs?**
6. **Does the program present conflict that a child can understand and does it demonstrate positive techniques for resolving the conflict?**
7. **Does the program stimulate constructive activities and does it enhance the quality of child's play?**
8. **Does the program separate fact from fantasy?**
9. **Does the program present humor at a child's level (no sarcasm or ridicule)?**
10. **Does the program have a pace that allows the child to absorb and contemplate the material presented?**
11. **Does the program have artistic qualities?**
12. **Has your child seen an appropriate amount of television for the day (remembering that a four or five year old tires with approximately one hour of viewing)?**

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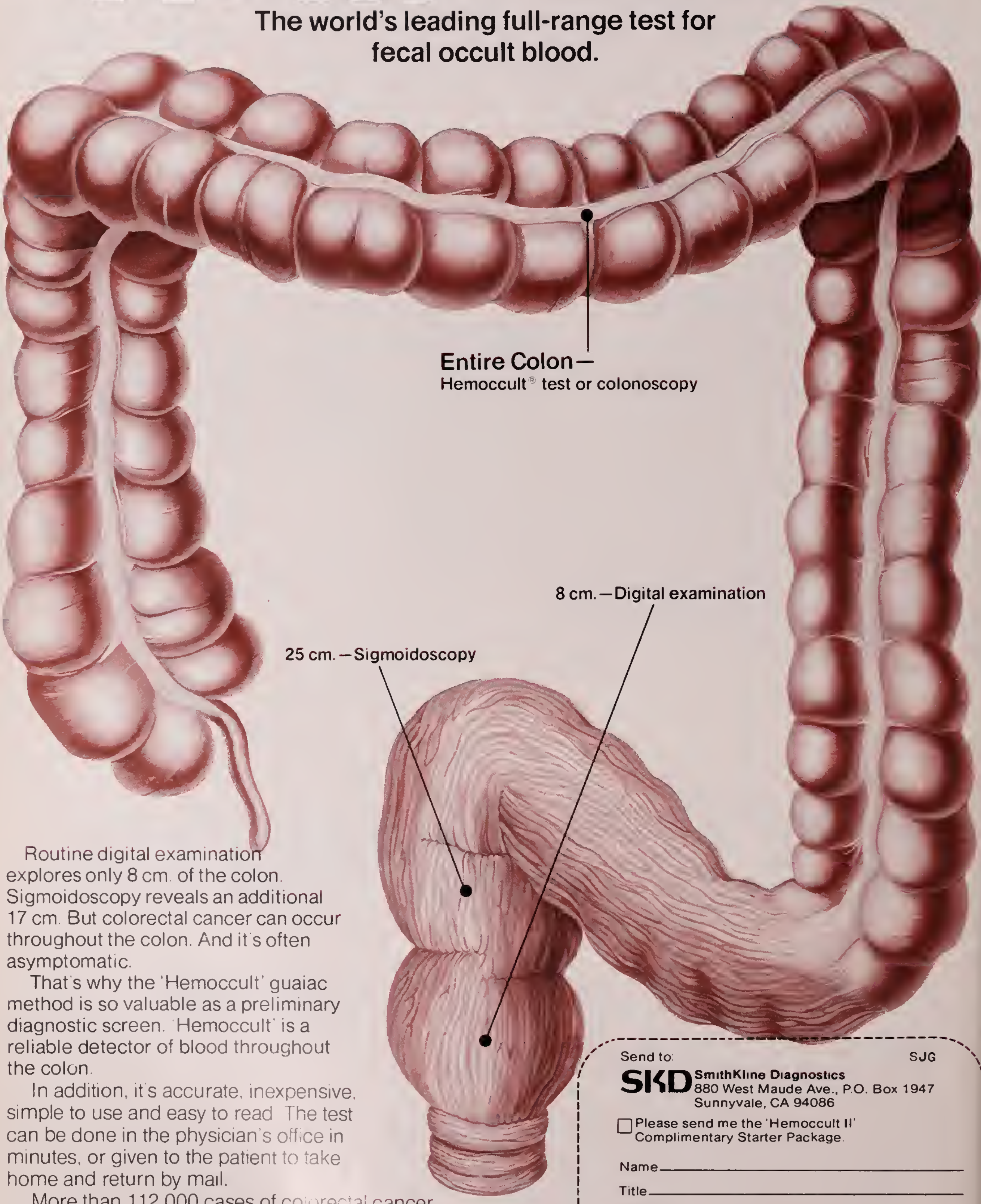

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Prospective Medicine

Role of Prospective Medicine in Health Care

THOMAS A. FENGER, Ph.D.*

The elusive "optimum health status" is indeed difficult to obtain. The historical medical model employed since the turn of the last century has made a significant impact; but only in the area of childhood infectious disease. For the most part adult chronic disease mortality and life expectancy have changed very little. The pursuit of improving life expectancy in the adult population must begin with a prospective approach. The patient (client) and health provider must examine and effectively deal with all of the recognizable potential health inhibitors. Such an examination process is termed Prospective Medicine. Prospective Medicine differs from the historical model of retrospective medicine in that it attempts to account for precursors to chronic types of disease states. Health providers must respond as catalytic agents in the promotion of health among their clientele. To effectively accomplish such a goal health providers must become as competent in diagnosing and treating for health as they are in diagnosing and treating for disease. The implementation of a chronic disease medical model and practicing medicine prospectively serve as effective mechanisms to accomplish this needed process.

PROSPECTIVE MEDICINE is of critical concern as the length of our life span becomes increasingly dependent upon "how" we live. In the United States, leading causes of death relate to individual lifestyle. Health professionals are beginning to promote responsibility for health. When citizens accept health responsibility, emphysema and lung cancer would almost completely disappear, death due to cancers would decrease by twenty-five percent, cirrhosis of the liver would become a rare disease, peptic ulcers, gastritis, esophagitis, pancreatitis, and atherosclerosis would occur less frequently. Without the help of the patient, medicine can make no such promises.[1]

Teaching and learning how to practice medicine prospectively require knowledge of the answers to these questions: (1) "What is killing American citizens?", (2) "What is hurting them?". and (3) "What can I do to make them feel better?". By analyzing these questions, we can formulate a new approach to medical practice. This new approach is termed Prospective Medicine.

Prospective Medicine begins not with an autopsy and asking, "Why did this patient die?". Rather, it begins by collecting health data on the client and asking the question, "How can I increase the life expectancy of this patient?".[2]

By using such an approach, health providers deal with precursors to disease and not merely the disease itself. As a result, thinking occurs on a prospective (preventive) basis as well as a retrospective (curative) basis. Prospective Medicine is futuristic rather than reactionary. The prospective process further emphasizes wellness.

Maintaining wellness, or health maintenance, is not a concept easily grasped by most practicing physicians. And why should it be? Physicians are in fact "doctors of disease"; they diagnose disease, treat disease, and receive their training in organizations filled with people suffering from the effects of disease. Because of such demands most physicians spend little time on health maintenance or wellness promotion. Those who are knowledgeable teach themselves or seek out others who are not usually directly associated with the practice of medicine. Some physicians, however, have had prospective medicine courses in medical school.

A Prospective Medicine course does not mean biostatistics or epidemiology. Instead it deals with health education methods and the concept of wellness. Wellness may be defined as the best compromise that can be made between the individual and his health concerns. Among the three leading killers in the

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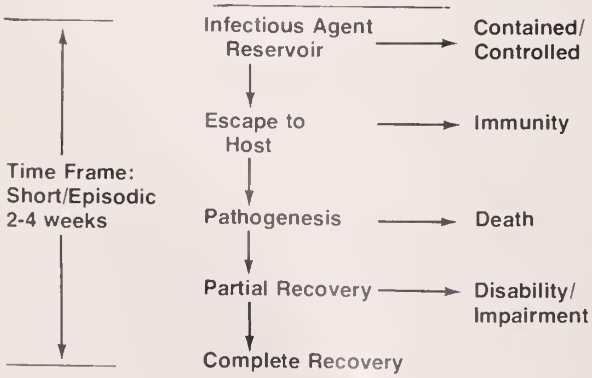
American population (heart disease, malignant neoplasms, and cerebral vascular lesions), we find such health risk factors as: elevated blood pressure and cholesterol levels, excessive pounds and lack of "girth control", inactivity, diets high in sodium, sugar and fat intake, and a general lack of health knowledge.[3] Many of these chronic disease precursors can be controlled by the individual.

If we stop to examine this proposition for a moment, we can readily see why Drs. Vickery and Fries in their new text, *Take Care of Yourself*, lead the text with the phrase "You can do more for your health than your doctor can".[4] It is true, *you* must be the one to control your dietary intake; *you* must be motivated to begin a regular exercise program; *you* must be the one to achieve a higher level of wellness.

Despite these positions the citizen "at large" sees the health provider as the "health expert" in charge of has/her personal health. Therefore, the primary health provider must be taught to promote patient health responsibility. Health professionals must become aware of the concept of Prospective Medicine and how this new medical model differs from the medical model of 1900.

The medical model used at the turn of the last century is not in tune with the 1970 chronic types of diseases. This classic disease model focuses upon the etiology of disease, usually as a single cause-effect phenomenon. For each disease or human impairment there is a single causitive agent, e.g. typhoid fever is caused by salmonella typhi, diphtheria is caused by corynebacterium diphtheriae, etc. With this approach, one logically follows the etiology or chain of events leading to the disease state in a given population. For example, s. typhi invades the community water supply; members of the community consume the water yielding an outbreak of typhoid fever among the local community members. Historically, at this point, the thinking has been to break the chain of events at the weakest link to stop typhoid epidemics. The algorithm of such a medical process would appear as follows:

Historic Medical Model

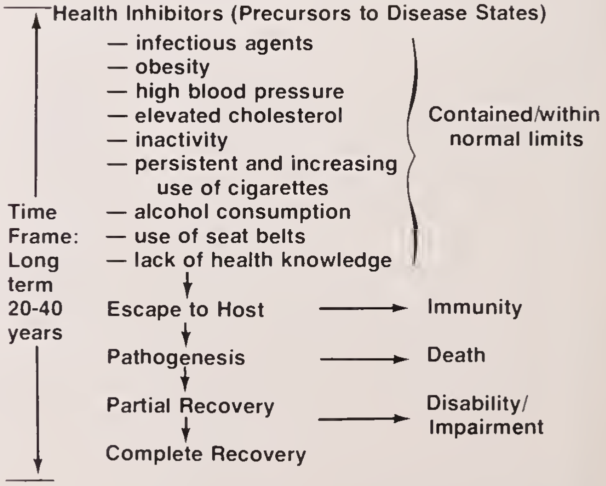

Infectious Agent Reservoir
Contained/ Controlled
Escape to Host
Immunity
Pathogenesis
Death
Partial Recovery
Disability/ Impairment
Complete Recovery
Time Frame: Short/Episodic 2-4 weeks

If we take the preceding medical model and apply it as we did at the turn of the century, we find our experience has been highly successful. In fact, this medical model has dramatically effected life expectancy. Life expectancy in the United States has risen a spectacular twenty-four years since the turn of the century; from 47 years in 1900 to 71.3 years today.[5] However, this improvement exists primarily because infectious childhood diseases are largely controlled. If one lived to be 30 years of age in 1900, he had 39.6 years of expected life remaining. If one lives to be the age of 30 today he can expect to live an additional 40.7 years.[6] This is an increase in life expectancy for the 30 year old person of only 1.1 *years* despite the advance in modern medical technology over the past 75 years. What are the reasons for such a dramatic increase in childhood life expectancy and not adult life expectancy?

The answer to such a question in part may be the historical medical model we incorporate as we practice medicine. The leading causes of death are no longer infectious as they were in 1900. The year 1900 saw health professionals combating leading health inhibitors as pneumonia, influenza, tuberculosis, diarrhea, and enteritis.[7] Today we have different leading causes of death; heart disease, cancers and stroke. Furthermore, it is relatively easy for physicians to treat infectious disease when they can pinpoint the causative agent.

Using the model of 1900 severely limits the options in promoting patient health. For example, are diseases of the heart caused by obesity, elevated cholesterol, high blood pressure, lack of exercise, or poor dietary control? Today's medical model can simply not employ techniques of the last century. Instead there is a multiple etiology of disease in the practice of modern medicine. Therefore today's medical model should appear as follows:

Chronic Disease Medical Model


Health Inhibitors (Precursors to Disease States)
— infectious agents
— obesity
— high blood pressure
— elevated cholesterol
— inactivity
— persistent and increasing use of cigarettes
— alcohol consumption
— use of seat belts
— lack of health knowledge
Contained/within normal limits
Escape to Host
Immunity
Pathogenesis
Death
Partial Recovery
Disability/ Impairment
Complete Recovery
Time Frame: Long term 20-40 years

There are two major differences between this model and its counterpart of 1900. First and most obvious is the number of potential health inhibitors or precursors to disease. Examining potential precursors to disease is the basis of practicing medicine prospectively. This examination process actually induces the health provider to promote orthobiosis (right style of living) in his practice. Thus the health provider's practice becomes truly involved in promoting health or wellness, as well as diagnosing and treating disease. Medical practice then becomes prospective (examination of precursors to chronic disease) plus retrospective (analysis of patient history, diagnosis and treatment). This process further encourages patients to become aware they have a role to play, related to the nature of their present health status. They must accept responsibility for their personal health.

Secondly, the time span jumps from weeks to years. The time span in our newly implemented medical model closely resembles the remaining life span after age 30. This may further indicate how lifestyle may effect personal health status and life expectancy.

It is at this juncture the difficulty begins in planning a regimen of treatment for health maintenance. For example, a person who has a high risk of heart disease may have a multiple treatment program such as; losing 20 pounds, jogging several miles a week, giving up smoking, and cutting down on saturated fat consumption. To be an effective and efficient catalyst, the physician must refer some of these responsibilities to ancillary health professionals such as health educators or nurse educators. Health program planning service should be initiated by the primary health provider. At this point many such health programs may be referred to the clinic health educator responsible for program planning and implementation.

At some point health providers must learn to pay more than mere lip service to the values of health maintenance. Our present health centers and clinics must begin to diagnose and treat for health as well as for disease.

The adoption of the chronic diseases model of medicine is perhaps a beginning in the direction of diagnosing and treating for health. This model allows for the establishment of the basic assumption that medicine can be practiced prospectively, not only retrospectively. Prospective medicine further recognizes that any client's health status must have positive input from the client as well as from his primary health provider. The health provider's role becomes one of motivating and assisting clients to become actively involved in their health as well as treating for all health inhibitors.

Many perceive the states of health and disease to be polarized as exact opposites. I propose that the states of health and disease are co-existent. Each of us may say we are 100 percent healthy and yet the aging process continues to place each of us in the terminally ill category. The relationship between health and disease, or prospective medicine and retrospective medicine is much like a glass, half of which contains a liquid. Do we say the glass is half empty or half full? It may be either, depending upon your perception. Is the asymptomatic man with an elevated blood pressure and cholesterol level healthy or diseased? Do we treat him prospectively or retrospectively?

In today's society with the leading causes of death in the United States being what they are, prospective medicine, health promotion, or health maintenance have their place along with retrospective medicine. One is not more important than the other; nor can optimum health status be achieved by the exclusion of one or the other.

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Index to Advertisers

American Heart Association 832
American Medical Association 794, 838
American Prosthetics, Inc. 832
Anderson, C. F. Co. 782
Burroughs-Wellcome Co. 784, 821
Classified Advertising 845
First Bank Minneapolis 793
Hearing Instrument Dispensers Guild 800
Lilly, Eli & Co. 770
Marquette National Bank . . . . Cover 2
Medical Protective Company 844
Mediclinics 772
Merrell-National, Inc. 830, 831, 832, 838, 839
Merck Sharp Dohme 794, 795, 796, 812
Metro Surgical Supplies, Inc. 802
Minnesota Medical Association 794
Purepac 781
Roche Laboratories . . . . 768, 782, 783, Cover 3, 4
Smith, Kline & French 829, 840
United Way 828
Upjohn Company 809, 810, 811, 812
Young and Company 798

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(Continued to page 846)

(Continued from page 845)

FAMILY PRACTITIONER, OB-GYN, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

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(Continued to Page 848)

(Continued from page 847)

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40	18	2 teasp. (10 ml)	1 tablet
60	27	3 teasp. (15 ml)	1½ tablets
80	36	4 teasp. (20 ml)	2 tablets or 1 DS tablet

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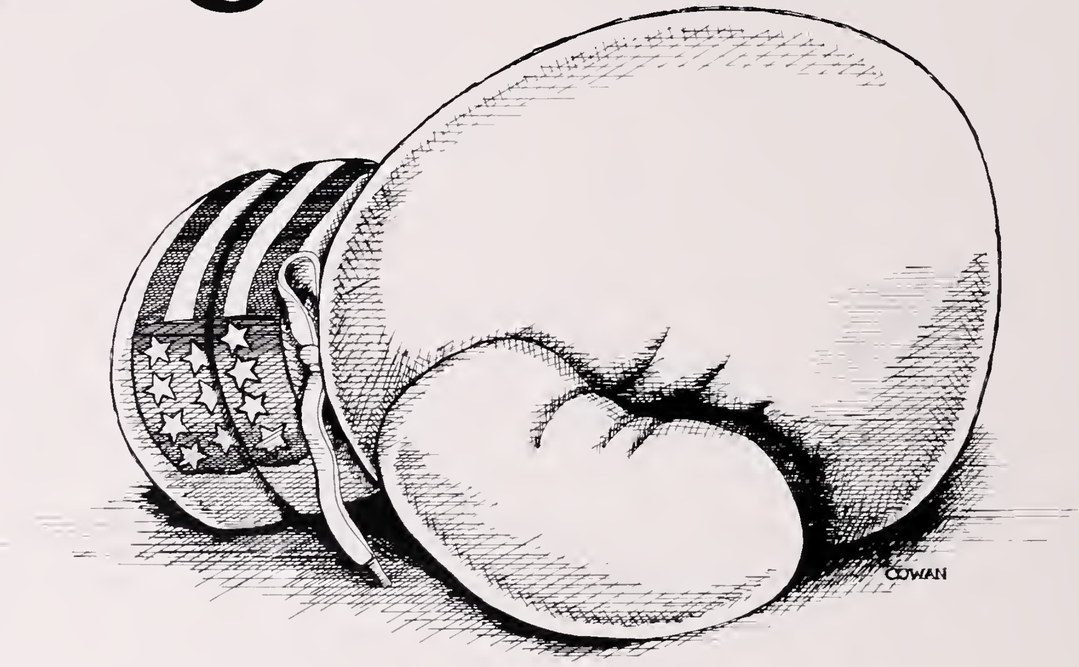

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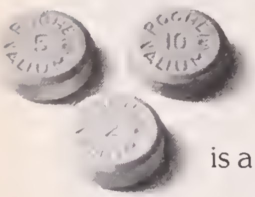
A character all its own.



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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults*. Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

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Contents — December, 1979

Volume 62:12
Pages 849-908

COVER PHOTOGRAPH — "Two Tall Ones in East Africa"
Oliver H. Peterson, M.D. 874

PRESIDENT'S LETTER
Frank E. Johnson, M.D.
President, Minnesota Medical Association 853

ORIGINAL CONTRIBUTIONS
1,000 Renal Transplants at the University of Minnesota 1963-1977
Bruce G. Sommer, M.D. et al. 861

INDO-CHINESE REFUGEES — Cultural Aspects in Working with Lao Refugees
Karen Olness, M.D. 871

LEGAL — Court Decision on United States vs. American Society of Anesthesiologists
Charles A. Geer, J.D. 855

SPECIAL ARTICLE — Surgery's Reawakening (1937-77)
Owen H. Wangensteen, M. D. 879

HISTORY — Thomas E. Keys . . . Medical Librarian, Historian, Scholar and Author — Extraordinarius
Jack D. Key, M.S., M.A. 883

MEDICINE GRAND ROUNDS — Laparoscopy in Internal Medicine
Lawrence R. Kaplan, M.D.
Editor: Robert J. McCollister, M.D. 889

FRACTURE CONFERENCE — Treatment of Ununited Fractures Adjacent to Joints
Frank C. Hui, M.D. et al. 895

NEUROLOGY — An Efficient Approach to the Mental Status Examination
Bruce D. Snyder, M.D. 901

RHEUMATOLOGY CORNER — D-Penicillamine in the Treatment of Rheumatoid Arthritis
Charles H. McKenna, M.D. 875

MINNESOTA MEDICAL ASSOCIATION — D-Day 1980
Richard C. Woellner, M.D. 856

CONTINUING MEDICAL EDUCATION 874, 882, 886, 905

CLASSIFIED ADVERTISING 894

NDEX TO ADVERTISERS 876

NDEX .... Index 1-6

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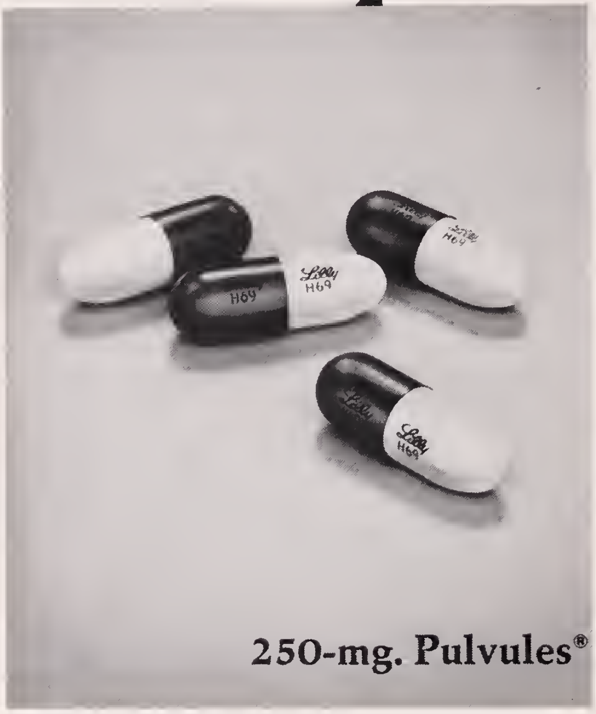

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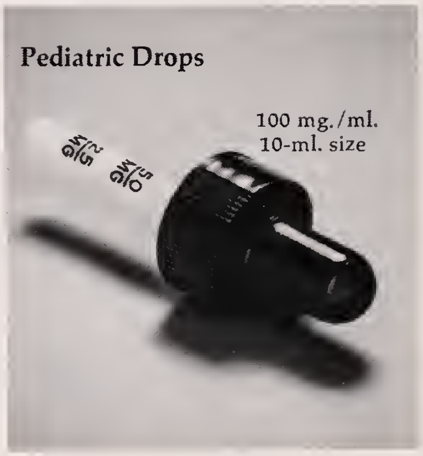

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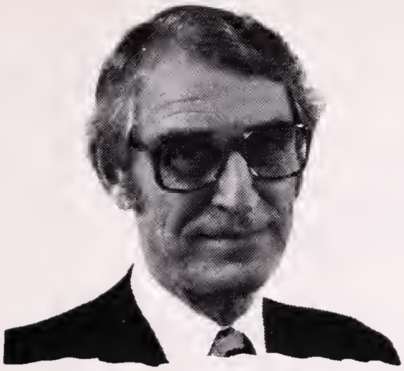

President's Letter

I continue to be concerned that while we, as individual practitioners, labor diligently to preserve the health of our patients, we are not showing the same concern nor exercising the same diligence in preserving the health and assuring the longevity of America. Each of us has a store of knowledge and armamentarium at our call which makes us more effective in the treatment of individual human ills than ever before in the history of the world. The feedback which we get from providing this service is instantaneously gratifying, both emotionally and materially. In fact, the emotional rewards are so pleasant and so strong that the practice of medicine may become truly addictive. It is understandable, therefore, that physicians may spend themselves completely in pursuit of their calling and fail to devote time, thought, or resource to the general health of America.

We are told that health care costs account for approximately 9 per cent of our gross national product. This amounts to an expenditure of some 200 billion dollars each year. The prudent management of such a sum of money is an awesome responsibility. America needs thoughtful reasoned opinions from physicians in order to make wise decisions regarding medical care. Such opinions are most persuasive when they result from a distillate of the thought of many individuals and carry the weight of the entire membership of our physician organizations. We are structured in a pyramid with county medical societies forming a broad base at the grass roots and rising through the states to the AMA. Each deals with problems at its own level, but information flows freely from the bottom to the top and back again. It goes without saying that if there were no state or AMA, the county societies, no matter how well each was organized, would be quite ineffective in dealing with state or national issues. Each component of the federation is vital to the strength of the whole.

As of this writing, the special obligation which physicians have to society is being borne by approximately half of those who are licensed to practice. Therefore, if you are one who belongs to the MMA, but not the AMA, please consider at once, shouldering your full share of the obligation by taking membership in the AMA. To those who have not joined us at any level, may I say that we dues-paying members are getting tired. We are tired of defending you and your practice from unwise health planning and excessive regulation. We are tired of advancing the cause of medicine without help from you. Our effort to help America suffers not only because we lack your financial support but our voice is weakened when we can speak for only half of the practicing physicians.

As an organization, the MMA intends to intensify its recruitment effort and make certain that we are supporting the federation at all levels. I hope that individual members will also aid in this effort in their daily contact with colleagues.

Frank E. Johnson

Frank E. Johnson, M.D.
President
Minnesota Medical Association

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Legal

Court Decision on United States vs. American Society of Anesthesiologists

CHARLES A. GEER *

Many physicians have indicated an interest in the recent court decision of *United States vs. American Society of Anesthesiologists* involving a relative value index and its possible effect upon the Consent Decree between Minnesota Medical Association and the Federal Trade Commission.

In the Anesthesiologists case, the New York Federal District Court rejected the contentions of the U.S. Justice Department and held that the promulgation of a relative value index by the American Society of Anesthesiologists did not constitute a *per se* violation of the Sherman Antitrust Act and did not violate that Act by being an unreasonable restraint of trade. In prosecuting its case, the Justice Department relied exclusively on a *per se* theory of violation of the Sherman Act, alleging that the existence and promulgation of a relative value index was itself an antitrust violation, regardless of the manner in which the index was used. Although the Justice Department appealed from the adverse decision, it recently dismissed the appeal. Counsel for the Anesthesiologists speculates that the appeal was dropped, at least in part, because of the possible adverse implications to the Government of having the opinion affirmed by a Circuit Court of Appeals.

Although the Anesthesiologists opinion undoubtedly represents an important victory for organized medicine, it must be taken in a fairly narrow context. We are advised by counsel to the Anesthesiologists that the government went so far as to concede that the Anesthesiologists had made no effort to coerce individual members into using the index. Further, the judge emphasizes that the Anesthesiologists developed their relative value index at the request and initiative of third party payors and the unique situation of Anesthesiologists in their not dealing with patients, having no competition and no opportunity for price discussion with their patients.

Unfortunately, the Anesthesiologists case has little, if any, relevance to the Consent Decree entered between Minnesota Medical Association and the FTC in 1978. The Anesthesiologists case was decided under the Sherman Antitrust Act, whereas the Consent Decree was entered under a completely different statute — the Federal Trade Commission Act. The former prohibits ''monopolies and restraints of trade;'' the latter prohibits ''unfair methods of competition . . . and unfair or deceptive acts or practices.'' Thus, the fact that the New York District Court determined that the Sherman Act had not been violated by the Anesthesiologists does *not* permit the inference that either the Anesthesiologists or the Minnesota Medical Association would not be found to have violated the Federal Trade Commission Act, even by the same judge.

Some have asked whether, in retrospect, the Minnesota Medical Association should have fought the FTC complaint and refused to enter the Consent Decree. We think that the decision to enter the Consent Decree is just as valid after the Anesthesiologists case as it was at the time made. First, the anticipated cost (in excess of one-half million dollars) of defending the FTC complaint was a significant deterrent; we are advised that the Anesthesiologists have already expended in excess of three-quarter million dollars in their defense. Second, the particular facts which surrounded the promulgation and use of the Minnesota relative value index were not nearly as helpful as those surrounding the Anesthesiologists' index. Third, the unique status of anesthesiologists relied upon so heavily by the New York judge distinguishes them from the cross-section of physicians represented by the Association.

---

*Attorney, Dorsey, Windhorst, Hannaford, Whitney and Halladay, Minneapolis, Minnesota

Minnesota Medical Association

D-Day 1980

IN SMOKING, as in the oil shortage, there is little debate that the problem exists. What we don't know is what to do about it. Last year 1,400 Minnesotans developed lung cancer, and 1,300 people died from it. Nation-wide 112,000 people developed lung cancer, and 98,000 died. Almost all of these developed their cancers because they smoked. More people were disabled by lung disease than by any other single cause except heart disease. The effects of smoking on heart disease, as well as on preexisting lung disease, are well known to everyone. Cigarettes also rank high as a cause of accidental fire deaths. Most smokers, and all physicians, know these problems that are caused by smoking, and all find it hard to quit smoking or to help others to do so.

The demand for help in smoking cessation has generated many solutions. Excellent voluntary and commercial group programs are available. Individual counseling efforts, threats, warnings and harassment all have their place in helping smokers abandon their destructive habit. Minnesota has made a unique contribution to this national effort: a Monticello newspaper editor, Lynn Smith, in 1974 began a state-wide health project to encourage smokers to quit for at least one day — "D-Day." This program has spread and is celebrated nationally. In Minnesota the D-Day project is annually supported by a host of agencies including the Minnesota Medical Association, and is sponsored by the Minnesota Lung Association and the Minnesota Division of the American Cancer Society, which provide financial support.

The next D-Day will occur Thursday, January 24, 1980. This year's campaign will be especially directed toward teenagers, who continue to increase their smoking habits, and to pregnant women who, by smoking, risk not only harm to themselves, but also to their yet-to-be-born children. The D-Day Committee will have a state-wide campaign to encourage smokers to quit on D-Day and will provide help to smokers who pledge to stop smoking for that day. Materials are available from them to help smokers quit.

We, as physicians, have a unique interest in preventative medicine and in helping our patients quit smoking. What can we do specifically to help?

1. We can, as always, provide specific logical and factual counseling about smoking to our patients.
2. We can have material on D-Day visible and offered to patients in our offices. Display stands for your office, posters, pledge cards, and information are all available from D-Day Headquarters, 614 Portland Ave., St. Paul, MN 55102 or by calling 612-227-8014.
3. We can remind smokers about D-Day and encourage them to pledge to quit then or at any time.
4. We can be an example and quit smoking ourselves.

Join the crowd — Quit smoking on January 24.

Richard C. Woellner, M.D.
Chairman, Professional Education Committee
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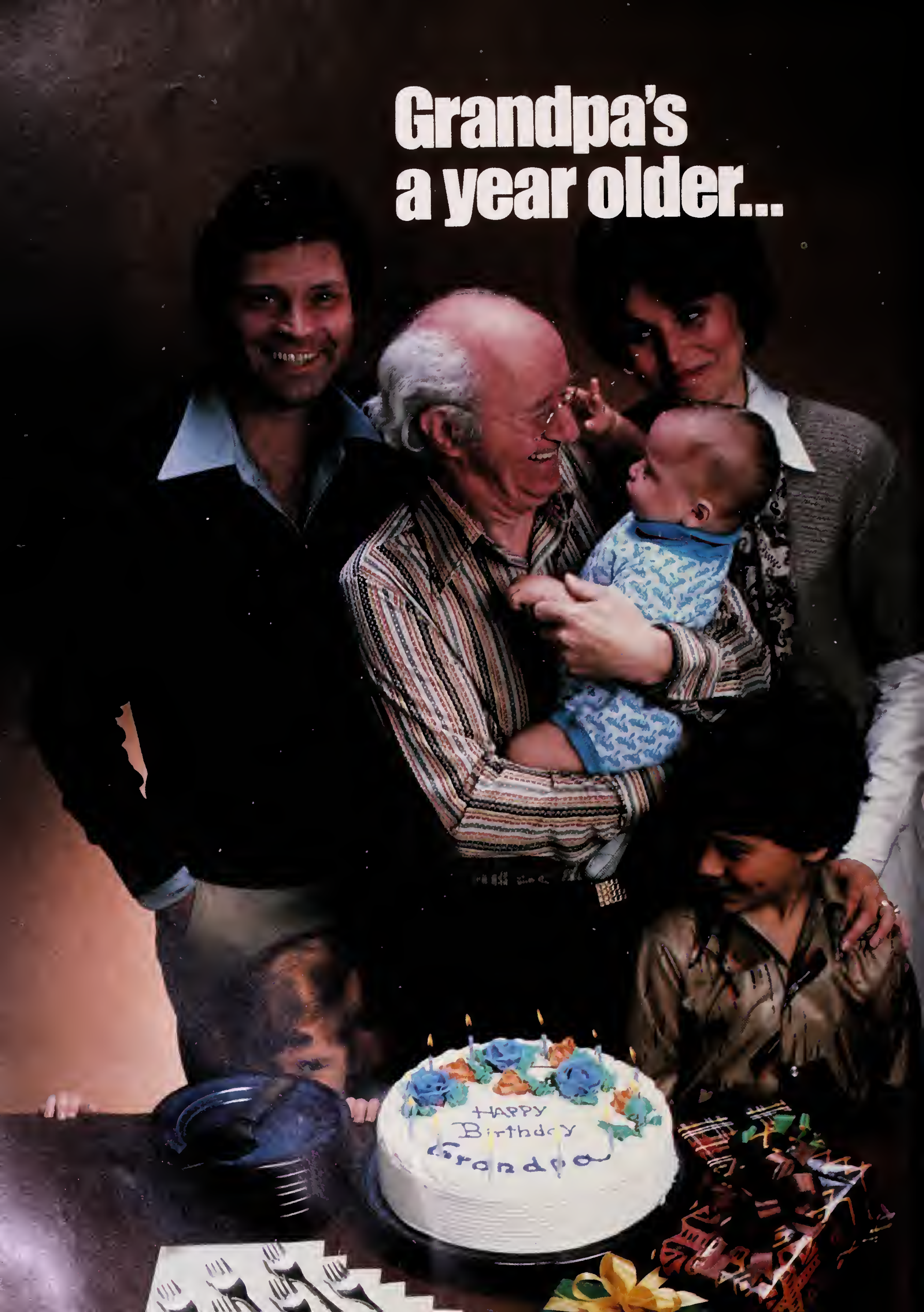
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(Pneumococcal Vaccine, Polyvalent MSD)

INDICATIONS: PNEUMOVAX is indicated for immunization against lobar pneumonia and bacteremia, caused by those types of pneumococci included in the vaccine, in all persons two years of age or older in whom there is an increased risk of morbidity and mortality from pneumococcal pneumonia. These include: (1) persons having chronic physical conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders; (2) persons in chronic care facilities; (3) persons convalescing from severe disease; (4) persons 50 years of age or older.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine. Epinephrine injection (1:1000) must be immediately available should an acute anaphylactoid reaction occur due to any component of the vaccine.

Do not give PNEUMOVAX to pregnant females; the possible effects of the vaccine on fetal development are unknown.

Children less than two years of age do not respond satisfactorily to the capsular types of PNEUMOVAX that are most often the cause of pneumococcal disease in this age group. Accordingly, PNEUMOVAX is not recommended in this age group.

PNEUMOVAX is not recommended for patients who have received extensive chemotherapy and/or nodal irradiation for Hodgkin's disease.

WARNINGS: *PNEUMOVAX will not immunize against capsular types of pneumococcus other than those contained in the vaccine (see table below).*

14 Pneumococcal Capsular Types Included in PNEUMOVAX

Nomenclature	Pneumococcal Types													
U.S.	1	2	3	4	6	8	9	12	14	19	23	25	51	56
Danish	1	2	3	4	6A	8	9N	12F	14	19F	23F	25	7F	18C

If the vaccine is used in persons receiving immunosuppressive therapy, the expected serum antibody response may not be obtained. Intradermal administration may cause severe local reactions.

PRECAUTIONS: Any febrile respiratory illness or other active infection is reason for delaying use of PNEUMOVAX, except when, in the opinion of the physician, withholding the agent entails even greater risk.

Caution and appropriate care should be exercised in administering PNEUMOVAX to individuals with severely compromised cardiac and/or pulmonary function in whom a systemic reaction would pose a significant risk and also to patients who have had episodes of pneumococcal pneumonia or other pneumococcal infection in the preceding three years and may have high levels of preexisting pneumococcal antibodies which may result in increased reactions, mostly local but occasionally systemic. Available data suggest that revaccination before three years may result in more frequent and severe local reactions at the site of injection, especially in persons who have retained high antibody levels.

Children under two years of age may not obtain a satisfactory antibody response to some pneumococcal capsular types. Therefore, the vaccine should not be used in this age group.

ADVERSE REACTIONS: Local erythema and soreness at the injection site, usually of less than 48 hours' duration, occurs commonly; local induration occurs less commonly. In a study of PNEUMOVAX (containing 14 capsular types) in 26 adults, 24 (92%) showed local reaction characterized principally by local soreness and/or induration at the injection site within 2 days after vaccination. Low-grade fever (less than 100.9°F) occurs occasionally and is usually confined to the 24-hour period following vaccination. Although rare, fever over 102°F has been reported.

Reactions of greater severity, duration, or extent are unusual. Rarely, anaphylactoid reactions have been reported.

NOTE: Administer subcutaneously or intramuscularly. *DO NOT GIVE INTRAVENOUSLY. DO NOT GIVE INTRADERMALLY.*

STORAGE AND USE: Store single-dose prefilled syringes and unopened and opened vials at 2-8°C (35.6-46.4°F). The vaccine is used directly as supplied. No dilution or reconstitution is necessary. Phenol 0.25% added as preservative.

Use a separate heat-sterilized syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another. All vaccine must be discarded after the expiration date.

Single-Dose Prefilled Syringe

Inject contents of syringe to effect a single dose.

Single-Dose and 5-Dose Vials

For Syringe Use: Withdraw 0.5 ml from vial using a sterile needle and syringe free of preservatives, antiseptics, and detergents.

HOW SUPPLIED: PNEUMOVAX is supplied in 5-dose vials of liquid vaccine, for use with syringe only; in a box of 5 individual cartons, each containing a single-dose vial of vaccine; and in 5 single-dose prefilled syringes.

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1,000 Renal Transplants at the University of Minnesota
1963-1977

BRUCE G. SOMMER, M.D.;* DAVID E. R. SUTHERLAND, M.D., PH.D.;* CARL M. KJELLSTRAND, M.D.*; RICHARD J. HOWARD, M.D., PH.D.*; S. MICHAEL MAUER, M.D.*; RICHARD L. SIMMONS, M.D.*; and JOHN S. NAJARIAN, M.D.*

Between June 7, 1963, and September 1, 1977, 1,000 renal transplants were performed at the University of Minnesota. On January 1, 1978, 70 per cent of the recipients were alive and 64 per cent had functioning grafts. The results of transplantation at a single institution are analyzed according to recipient risk factors and period of transplantation.

RENAL TRANSPLANTATION at the University of Minnesota Hospitals was first undertaken on June 7, 1963 by Dr. Richard L. Varco. On September 1, 1977, the 1000th transplant was performed at the same center by Dr. John S. Najarian. During the intervening 14½ years renal transplantation has become an accepted and effective method of treatment for end stage renal failure[1–4]

From 1963 to 1967, Dr. William Kelly and many other physicians collaborated in the pioneer venture of renal transplantation at the University Hospital.[5] In 1967 Dr. John S. Najarian assumed responsibility for the transplant service, and one year later, Dr. Carl M. Kjellstrand, a nephrologist, and Dr. Richard L. Simmons, a surgeon, joined the program. These three individuals formed the nucleus of a transplant team that has made the University of Minnesota one of the largest transplant centers in the world. The University of Minnesota experience with 1,000 transplants in 866 recipients and virtual 100 per cent followup is the basis for this report.

Patient Population and Methods

Between June 7, 1963, and September 1, 1977, 566 renal allografts from related donors and 434 renal allografts from cadaver donors were transplanted to 866 patients (499 males and 367 females). There were 853 first, 128 second, 15 third and 4 fourth transplants. Thirteen patients (11 nondiabetic and 2 diabetic) had their first transplants elsewhere. One patient had a second transplant elsewhere, but a first and third transplant at the University of Minnesota. The ages of the recipients at the time of transplantation ranged from six weeks to 72 years.

Approximately 3 per cent of all patients referred to the University of Minnesota during this time span for treatment of end stage renal failure have not been transplanted because of: (a) the presence of malignancy, (b) extreme age, (c) multiple severe complications of diabetes mellitus and other systemic diseases, (d) the presence of cytotoxic antibodies to potential donors, or (e) the patients' preference for chronic hemodialysis.

Prior to 1968, patients were selected for transplantation on the basis of factors believed to place them in a good risk category. Since 1968 liberal criteria have been used, and many patients categorized as "high risk" have received kidney transplants.[6–8] During the last seven years an increasing proportion of patients with diabetes mellitus,[9–10] collagen diseases,[11] enzyme deficiencies,[12] vascular disease and urinary tract anomalies[13] have been transplanted. The commitment

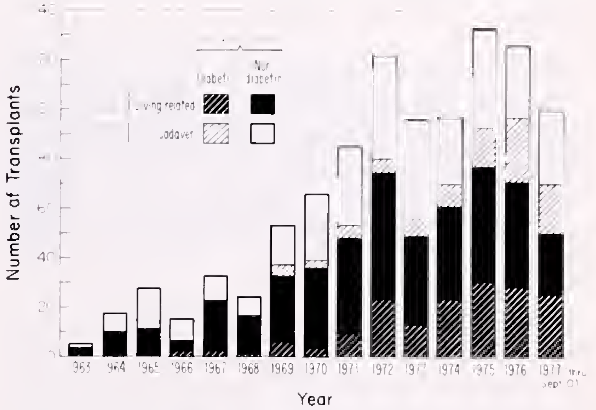

Fig. 1 — Renal transplants at the University of Minnesota by year, donor source and presence or absence of diabetes, June 7, 1963 to September 1, 1977.

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to treat diabetic patients with chronic renal failure has been especially strong. Two hundred thirty-six patients had diabetes mellitus as the etiology of their renal failure. Figure 1 depicts the number of transplants performed each year according to donor source, and illustrates the increasing number of diabetics transplanted since 1970.

Patients are referred to the University of Minnesota in all stages of renal failure. Some have been on dialysis for years, while others begin dialysis after referral. Most patients who have related donors are transplanted within two to four weeks of evaluation. The procedure for selection of related donors and the pretransplant preparation of the recipient have been previously described.[14] Patients who have no suitable related donors are placed on a waiting list and are treated at hemodialysis units near their home until a cadaver kidney becomes available. Since 1969, tissue typing of donors and recipients for HLA antigens has been routinely performed and has been used for retrospective analysis of the effect of donor and recipient matching on the results of transplantation.[15–17]

From 1963 to 1969, organ removal from cadaver donors and preparation of the recipient for transplantation were performed simultaneously in the operating room. The kidney function of donors who had died from cardiac arrest was maintained by whole body perfusion with the heart lung machine. Since 1970, kidneys from brain dead cadaver donors have been preserved by hypothermic pulsatile perfusion,[18,19] which allows organs to be shared between transplant centers, tissue typing to be performed before transplantation, and for recipients to be selected according to HLA compatibility with the donor. Since 1970, approximately 70 per cent of all cadaver kidneys used at the University Hospitals have come from Minnesota (Table 1).

TABLE 1

Source of Cadaver Kidneys Transplanted at the University of Minnesota

University of Minnesota	16%
Twin Cities Hospitals	38%
Minnesota Outside of Twin Cities	18%
Out of State	28%

Most transplants have been performed with a standard technique. The kidney is placed in the iliac fossa with vascular anastomoses to the iliac vessels and a ureteroneocystostomy. Before 1969, the immunosuppressive regimen consisted of azathioprine and prednisone. Since 1969, antilymphocyte globulin has been given in the immediate posttransplant period.[20]

We have calculated the overall percentage of patients and grafts surviving as of January 1, 1978 (four months to 14½ years followup). In addition, actuarial methods[21] were used to construct cumulative survival curves for patient survival and graft function, which gives a more accurate expression of the results obtained. All causes of death are included in the survival charts. Loss of graft function is defined by return to maintenance dialysis or death. Grafts lost for technical reasons or from hyperacute rejection are included in the analyses. Although some patients have been followed for more than 14 years, no curves are extended to beyond seven years.

Results

At the time of this review, 601 patients (70 per cent) were alive and 550 (64 per cent) have functioning grafts. Table 2 summarizes the number of first transplants according to donor source and the current overall patient and primary graft survival. Table 3 summarizes the overall results of second, third, and

TABLE 2

First Transplants University of Minnesota According to Donor Source and Recipient Status Overall Function and Survival*

Donor Source	Number of Transplants	Percent Recipients Surviving	Percent Grafts Functioning
RELATIVE	514	76	65
HLA Identical Siblings	112	90	88
Other Related†	402	73	58
CADAVER	339	60	48
⩾2 AGN match	139	77	65
⩽1 AGN match	200	48	36
TOTAL	853	70	58

*As of January 1, 1978 — 4 months to 14½ years followup

†Includes non HLA identical sibling (150), parent (171), child (53), and distantly related (28) donors

TABLE 3

Overall Results of Retransplantation after Loss of First Graft*

	Number of Transplants	Percent Recipients Surviving	Percent Grafts Functioning
LIVING RELATED DONOR	52		
Second Transplant†	48	73	41
Third Transplant	4	50	25
CADAVER	95		
Second Transplant	80	53	33
Third Transplant	11	73	64
Fourth Transplant	4	50	25
TOTAL	147	60	37‡

*As of January 1, 1978 — 4 months to 14½ years followup

†Includes one HLA identical donor

‡The 147 transplants were done in 129 patients. Of the 78 patients currently alive after retransplantation 55 (71%) have functioning grafts.

fourth transplants according to whether related or cadaver donor kidneys were used. The majority of donors for subsequent transplants have been cadavers. Although the percentage of patients and grafts currently surviving after primary transplantation (Table 1) and retransplantation (Table 2) appear similar, the average length of followup is shorter after retransplantation. In actual fact the results after retransplantation are less good than after primary transplantation. These differences are apparent in the cumulative survival curves described in the following sections.

First Transplants

The patient survival of all recipients is plotted in Figure 2 according to the length of followup without regard to donor source or the period of transplantation. At two years, 75 per cent of the recipients are alive; by seven years 64 per cent of all recipients are alive. The reported survival of patients treated by chronic hemodialysis in America and Europe is also included in this figure.[22,23]

Three important factors in determining the outcome of transplantation are: (a) donor source (Figure 3), (b) the age of the recipient (Figure 4), and (c) presence or

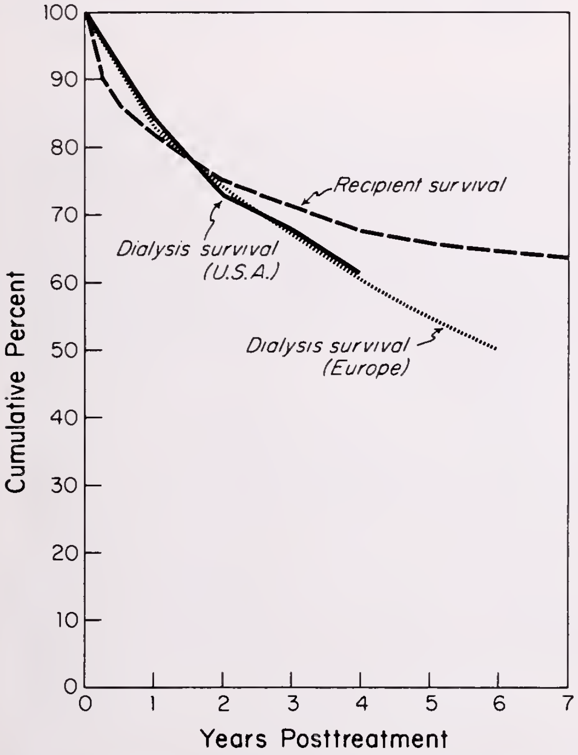

Fig. 2 — Patient survival of all 853 primary renal transplant recipients (1963-1977) without regard to donor source or other risk factors; compared to reported survival for patients on chronic hemodialysis in America[22] and Europe.[23]

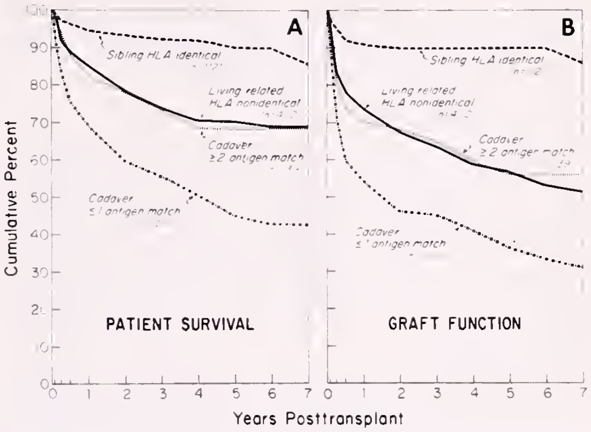

Fig. 3 — Patient survival (A) and graft function (B) after primary transplantation in recipients of kidneys from HLA identical siblings, other relatives, and cadavers sharing ≤ 1 or ≥ 2 HLA antigens with the recipient; without regard to age or presence or absence of diabetes; 1963-1977.

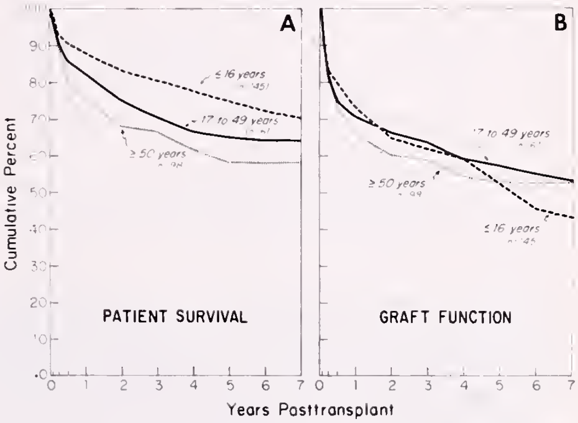

Fig. 4 — Patient survival (A) and graft function (B) after primary transplantation in three age groups, without regard to donor source or presence or absence of diabetes in the recipient; 1963-1977.

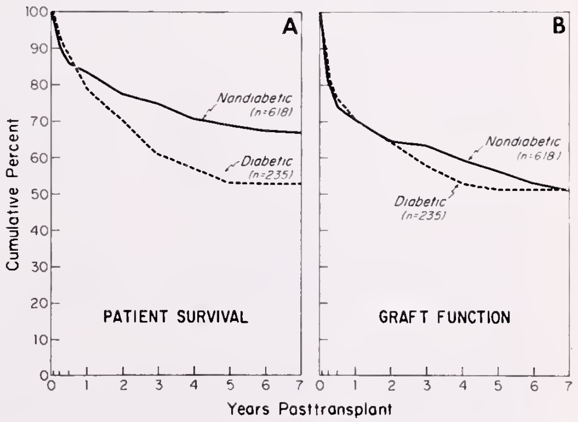

Fig. 5 — Patient survival (A) and graft function (B) after primary transplantation in diabetic and nondiabetic patients without regard to donor source or age of the recipient; 1963-1977.

absence of diabetes in the recipient (Figure 5). The impact of each of these variables on patient and graft survival has been analyzed separately.

Effect of Donor Source

In Figure 3, patient and primary graft survival are plotted separately for transplants from phenotypically HLA identical siblings (perfect match), from other related donors, from well matched cadaver donors (sharing ⩾ 2 HLA antigens with the recipients), and from less well matched cadaver donors (sharing ⩽ 1 HLA antigen).

Recipients of kidneys from HLA identical siblings rarely lose their grafts and they have the best patient survival (93 per cent at two years and 86 per cent at seven years). Patient and graft survival for recipients of kidneys from other related donors is similar to that of recipients of well matched cadaver kidneys.

Patient survival is 78 and 68 per cent at two and seven years after transplantation of kidneys from relatives other than HLA identical siblings. Further subdivisions can also be made in this group according to whether the donor is a child (n = 53), parent (n = 171), HLA nonidentical sibling (n = 150), or nonimmediate family member (n = 28) of the recipient. When these subgroups are analyzed separately, the patient and graft functional survival from child to parent, parent to child, and HLA nonidentical sibling to sibling transplants are not significantly different (curves not shown). The only subgroup which does significantly less well than any of the others are those patients receiving grafts from distantly related donors; graft survival is 10 per cent less at two years and 15 per cent less at seven years than for recipients of kidneys from donors from the immediate family (HLA identical siblings excluded). The uniform results obtained with the various categories of immediate family HLA nonidentical donors is not surprising, because the histocompatibility differences in each of these groups are generally similar. All recipients of parent or child kidneys differ by one HLA haplotype from the donors; a majority of the HLA nonidentical sibling donors also differ by one haplotype, although a few (< 15 per cent) were matched for neither haplotype (complete mismatch).

Differences in patient and graft survival are also apparent when recipients of cadaver kidneys are subdivided according to the HLA match with the donor. Recipients of cadaver grafts matched for ⩽ 1 HLA antigen with the donor do less well, but recipients of cadaver grafts from donors matched for ⩾ 2 HLA antigens do almost as well as recipients of related grafts. In recipients of well matched cadaver kidneys, patient survival is 75 and 69 percent at two and seven years after transplantation. The differences in results between well and poorly matched recipients of cadaver grafts are similar to those reported in our previous analyses.[16,24]

Effect of Age

In Figure 4, patient and primary graft survival are plotted separately for three age groups (⩽ 16, 17 to 49 and 50 to 72 years old) without regard to donor source or diabetic status. Graft survival in the intermediate age group is better than in either extreme. The differences would be even more pronounced if recipients with diabetes were not included in the analysis, because all but five of the diabetic recipients are in the intermediate age group. However, patient survival after transplantation is better in the younger patients. Both patient and graft survival are less good in the older age group.

Effect of Diabetes

In Figure 5, patient and primary graft survival are plotted separately for diabetic and nondiabetic recipients, without regard to donor source or recipient age. Patient and graft survival is better in nondiabetic than diabetic patients, e.g., at two years, survival of nondiabetic patients is 77 per cent and in diabetic patients is 70 per cent. This difference is consistent with our earlier analysis of transplantation in diabetic patients.[9,10]

Retransplantation after Loss of First Graft

Patient survival and graft function after a second transplant are shown in Figure 6. When the second kidney is from a related donor, 72 per cent of the patients are alive at two years and 65 per cent of the grafts are functioning. When a cadaver kidney is used for the second transplant, 55 per cent of the recipients

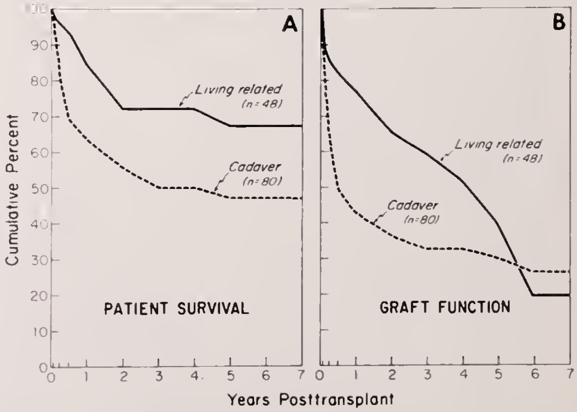

Fig. 6 — Second transplant patient survival (A) and graft function (B) in recipients of kidneys from related and cadaver donors, without regard to age or presence or absence of diabetes; 1963-1977.

are alive at two years and 36 per cent of the grafts are functioning. Only 14 of the 128 patients receiving second transplants had diabetes mellitus; six of these patients are currently alive and four have functioning grafts.

Cumulative patient and graft survival two years after transplantation in the 14 recipients of third kidneys is 56 per cent and 48 per cent respectively. Only two of the four patients who received a fourth transplant are alive, and only one has a functioning graft.

Time Division

Because the results of transplantation and dialysis have improved since 1963, the patient and graft survival results for the entire span of 14 years (Figures 2-6) do not reflect the probability with which kidney function can be reestablished, or survival achieved, by transplantation today in patients with chronic renal failure. To emphasize this point we have analyzed the results of transplantation separately for three periods (I-1963-1967; II-1968-1971; III-1972-1977) during the evolvement of transplantation at the University of Minnesota (Table 4). Figure 7 shows the patient survival for recipients of kidneys from (a) HLA identical sibling, (b) other related, (c) cadaver ≥ 2 antigen matched, and (d) cadaver ≤ 1 antigen matched donors during the different periods. The survival of

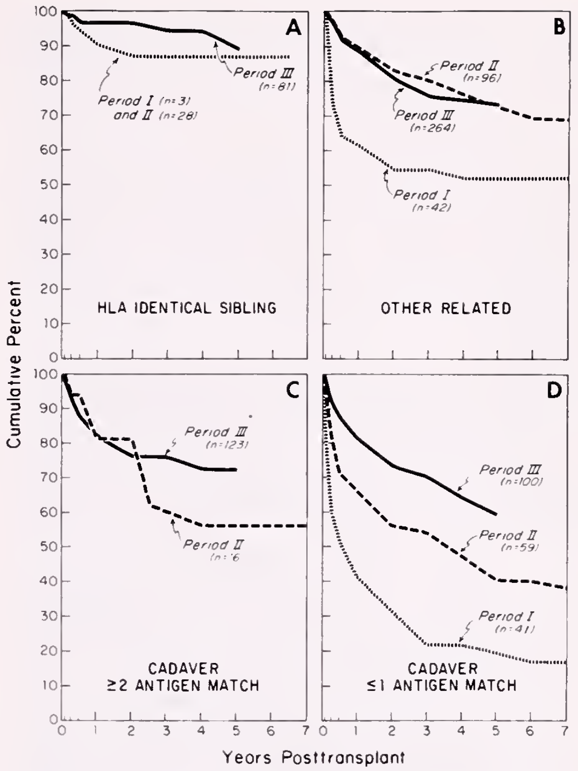

Fig. 7 — Patient survival according to donor source and HLA match in recipients of kidneys transplanted during Period I (1963-1967), Period II (1968-1971) and Period III (1972-1977).

TABLE 4

Minnesota Renal Transplant Experience 1963-1977

Period	Dates	No. LRD TX*	First Transplant 2 Year Cumulative (%) Patient Survival	First Transplant 2 Year Cumulative (%) Graft Function	No. CAD TX*	First Transplant 2 Year Cumulative (%) Patient Survival	First Transplant 2 Year Cumulative (%) Graft Function	Period Characteristics
I	June 1963- Dec. 1967	50 (45)	58	56	48 (41)	32	20	—Azathioprine/Prednisone —No or incomplete tissue typing —Cardiopulmonary bypass whole body preservation for cadaver donors —Good risk patients
II	Jan. 1968- Dec. 1971	133 (124)	85	77	96 (75)	61	51	—Azathioprine/Prednisone/ALG —Improved tissue typing —Brain dead heart beating cadaver donors —Pulsatile hypothermic organ preservation developed —All risk patients/few diabetics
III	Jan. 1972- Sept. 1, 1977	383 (345)	85	73	290 (223)	75	61	—Azathioprine/Prednisone/ALG —Good tissue typing and cytotoxic screening —Organ sharing because of preservation capabilities —All risk patients/many diabetics

LRD TX are Living Related Donor Transplants
CAD Tx are Cadaver Donor Transplants
*Numbers in parentheses are first transplants

patients receiving HLA identical sibling kidneys has been excellent in all periods, and shows what can be achieved with transplantation when the immunological barrier is minimal.

The survival of patients receiving kidneys from other related donors has improved since 1968, and reflects the changes in organization and patient management that are detailed in Table 4. However, between Period II and Period III, the results of transplantation have not changed significantly in this group.

Patient survival has improved progessively for recipients of cadaver kidneys matched for either ≥ 2 or ≤ 1 antigen with the donor. Currently (Period III), two year patient survival for recipients of ≥ 2 antigen matched cadaver grafts is 76 per cent and for recipients of ≤ 1 antibody matched cadaver grafts is 73 per cent. Current graft functional survival at two years is 67 per cent and 56 per cent respectively for recipients of cadaver grafts matched for ≥ 2 and ≤ 1 antigen with the donor (graft survival curves not shown).

Because of our emphasis on treating diabetics with end stage renal failure during recent years, the results of transplantation in the different periods are presented separately for diabetic and nondiabetic recipients (Figure 8). In contrast to the stabilization of survival of nondiabetic recipients of related grafts between Periods II and III, the survival of diabetic patients of related grafts has improved substantially (from 58 per cent to 75 per cent at two years). Current (Period III) primary graft survival at two years for diabetic recipients of related kidneys is 73 per cent. The corresponding two year patient and graft survival figures for nondiabetic recipients of related kidneys are 89 per cent and 73 per cent respectively.

The increase in survival between Periods II and III after transplantation of cadaver kidneys to diabetic patients is even greater than for diabetic recipients of related kidneys. Two year patient survival for diabetic recipients of cadaver kidneys during Period II was 33 per cent and during Period III was 70 per cent. Current graft survival for diabetic recipients of cadaver kidneys is 55 per cent. One explanation for the large differences between Period II and III is the fact that seven diabetic recipients of cadaver kidneys in Period II also received concurrent whole pancreas transplants — a high risk procedure that has not been performed in Period III.

Currently (Period III), the two year patient and graft survival for nondiabetic recipients of cadaver kidneys is 77 per cent and 63 per cent respectively. These figures show that diabetic recipients now do almost as well as their nondiabetic counterparts (only 7 and 8 per cent differences in patient and graft survival at two years).

Patient and Graft Survival According to Combined Risk Factors

Separate analysis of the transplant population according to single risk factors is useful in determining the impact of each factor. For an individual patient, however, the risk factors occur in various combinations. To calculate the chances of surviving or maintaining graft function after transplantation, we divided the 853 recipients of primary grafts into subgroups according to the combinations of the major risk factors (donor source, histocompatibility match, age and diabetes) and constructed actuarial survival curves for each subgroup. Table 5 summarizes the two year patient survival and graft function for all subgroups that consisted of at least 20 patients. Obviously, nondiabetic recipients in the intermediate age group who have HLA identical sibling donors do best, while patients > 50 years old who receive poorly matched cadaver kidneys do the least well. Other combinations will fall in between these two extremes, the positions of the survival curve depending on which

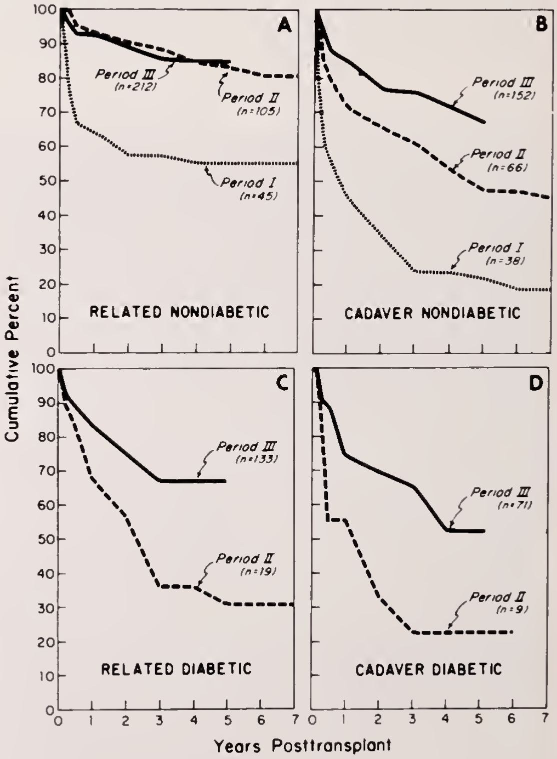

Fig. 8 — Patient survival in nondiabetic (A,B) and diabetic (C,D) recipients of related (A,C) and cadaver (B,D) kidneys transplanted during Period I (1963-1967), Period II (1968-1971) and Period III (1972-1977). Only three diabetic patients were transplanted in Period I; all died by 6 months (curve not shown).

of the variables are combined. Because the analysis includes the patients from all three periods, the survival figures are lower than what can actually be achieved by transplantation today.

Discussion

Transplantation and hemodialysis are integrated at the University of Minnesota. Patients with chronic renal failure are treated with dialysis until transplantation can be done. If a graft is rejected, the patient is returned to hemodialysis — either indefinitely or until retransplantation. With this approach, optimal patient survival with maximal rehabilitation can be achieved.

Analysis of the first 1,000 transplants performed at the University show the influence of three main risk factors on patient survival and graft function: (a) donor source and histocompatibility match with the recipient; (b) age of the recipient; and (c) presence or absence of diabetes.

In regard to donor source, transplantation from HLA identical siblings is the most successful. Transplants from other related donors are clearly more successful than transplants from cadaver donors that are poorly matched with the recipients. When all three periods are analyzed together (Figure 3), patient survival and graft functional survival appear to be similar for recipients of kidneys from HLA nonidentical related donors and recipients of kidneys from well matched cadaver donors. However, all of the recipients of kidneys from cadaver donors matched for ≥ 2 HLA antigens were transplanted in Periods II and III, while the group receiving HLA nonidentical related kidneys includes patients transplanted in all three periods. A more valid comparison of patient and graft survival between these two groups can be made by analysis of single periods. For example, in Period II, the patient survival at two years is 85 per cent for recipients of kidneys from HLA nonidentical related donors and 81 per cent for recipients of well matched cadaver kidneys. Two year graft survival in these two groups is 74 per cent and 69 per cent respectively. The same relative differences in patient and graft survival between recipients of kidneys from HLA nonidentical related donors and well matched cadaver donors are seen in Period III.

The differences in survival between well and poorly matched cadaver allograft recipients was recognized in our previous analyses.[16,24] Therefore our present policy for patients waiting for cadaver kidneys is to delay transplantation until a kidney is available from a donor that shares two or more HLA antigens with the recipient. Patient survival and graft survival in recipients of allografts from distantly related donors is also not as good as when the donors are from the immediate family or from cadavers well matched with the recipient. For this reason, our general policy now is to transplant cadaver kidneys if a parent, child, or sibling cannot be the donor. Although the differences in patient and graft survival between recipients of kidneys from HLA nonidentical related (immediate family) and well matched cadaver donors are slight, we

TABLE 5

Actuarial Recipient Survival and Graft Function at Two Years In Patients Divided into Subgroups* Based on Combinations of Three Variables: Age, Graft Source, Presence or Absence of Diabetes

			First Transplant 2 Year Cumulative (%)	
Donor Source	**Recipient Status**	**Age of Recipient**	**Patient Survival**	**Graft Function**
HLA Identical Sibling	Nondiabetic Sibling	17-49	98	92
Related Child	Nondiabetic Parent	> 50	91	79
Related Child	Nondiabetic Parent	17-49	89	80
HLA Identical Sibling	Diabetic Sibling	17-49	87	86
Related Parent	Nondiabetic Child	≤ 16	87	65
Cadaver ≥ 2 AGN match	Nondiabetic	17-49	84	59
HLA Nonidentical Sibling	Nondiabetic Sibling	17-49	82	68
Related Parent	Diabetic Child	17-49	82	81
Related Parent	Nondiabetic Child	17-49	75	64
Distantly Related	Nondiabetic Distant Relative	17-49	72	61
Cadaver ≥ 2 AGN match	Diabetic	17-49	69	60
HLA Nonidentical Sibling	Diabetic Sibling	17-49	67	62
Cadaver ≤ 1 AGN match	Nondiabetic	≤ 16	65	48
Cadaver ≥ 2 AGN match	Nondiabetic	≥ 50	60	55
Cadaver ≤ 1 AGN match	Nondiabetic	17-49	59	47
Cadaver ≤ 1 AGN match	Diabetic	17-49	53	39
Cadaver ≤ 1 AGN match	Nondiabetic	≥ 50	45	35

*All groups contain ≥ 20 patients

believe related donors should be used whenever possible because the number of cadaver organs is limited.

The relative differences in patient survival and graft function according to donor source and histocompatibility match with the recipient detected in our analysis are similar to those reported from other centers[25,26] and from the American College of Surgeons/National Institutes of Health (ACS/NIH) Renal Transplant Registry.[27,28] Although the overall results of transplantation from both cadaver and related donors at the University of Minnesota are better than those apparent in the pooled data reported by the ACS/NIH Renal Transplant Registry,[27,28] other centers have achieved patient survival results equivalent to our own.[1,3]

The second major risk factor analyzed in this report is age of the recipient. When calculated independently of donor source and the presence or absence of systemic disease, patient survival rates are highest for the younger age group ($\leqslant$ 16 year old) and lowest for the old age group ($\geqslant$ 50 years old). Graft survival, however, is best in the intermediate age group. These results reflect the ability of children to tolerate graft loss.

To illustrate the influence of a systemic disease on the results of transplantation, we chose diabetes mellitus because of the large number of patients with this disorder in our series. Renal allograft recipients with diabetes mellitus do less well than those without diabetes. Patient survival is about 10 per cent less good at two years when the analysis is conducted independently of recipient age or donor source.

The findings that survival in certain groups of patients (those with diabetes mellitus or of an older age) is not as high as that in patients of optimal age without systemic disease does not mean that transplantation is less applicable as treatment for these groups. In general, patients in categories that do less well after transplantation also do less well when treated with chronic hemodialysis. For example, diabetic patients who receive a poorly matched cadaver kidney have a two year survival rate of only 53 per cent (Table 5); however, their survival is still better than that reported for chronic hemodialysis.[9,10,29,30] For nondiabetic recipients of related kidneys, the survival after transplantation is superior to that reported with chronic hemodialysis by the National and European Dialysis Registries, no matter what the age of the patient.[22,23] For nondiabetic recipients of cadaver kidneys, patient survival is as good as, or better than, that reported by the Dialysis Registries in the intermediate age groups (17 to 49 years old). For nondiabetic recipients older than 50 years, the survival after transplantation of cadaver kidneys is not better than that achieved with chronic hemodialysis alone.[22,23]

Our transplant survival figures include patients transplanted from 1963 to the present. While the dialysis figures cited for comparison consist mainly of patients who started dialysis after 1968.[22,23] The results of transplantation at Minnesota have improved since the first period (Table 4; Figures 7 and 8). From Period I (1963-1967) to Period II (1968-1971), two year patient survival for related kidneys increased by more than 25 per cent and graft functional survival almost doubled. For patients receiving cadaver kidneys patient survival increased by 20 per cent between Period I and II and graft functional survival more than doubled. The differences between Period I and II are even greater when only nondiabetics are analyzed. A significant number of diabetics were first transplanted in Period II, and the early results with transplantation in diabetics were not as good as they are now. Although the results in non-diabetic recipients of related kidneys did not change significantly in terms of patient survival and graft function between Periods II and III, significant improvement of patient survival and graft function did occur in diabetic recipients of related or cadaver kidneys and in all recipients of cadaver kidneys.

We feel that the increase in graft survival since 1967 can in part be attributed to the addition of antilymphocyte globulin to the immunosuppressive regimen. The use of HLA matching in donor selection has also been a factor. The large improvement in patient survival between these periods can be partially attributed to early decreases in the degree of immunosuppressive therapy, and the recognition that chronic rejection should not be treated aggressively. When a patient has repeated rejection episodes, we stop immunosuppressive therapy and return the patient to hemodialysis. This approach has reduced the risk of death from sepsis, and is the policy now followed by most other transplant centers.[1,2,3] The continual improvement in the results in diabetic patients reflects our increased experience in managing their special problems.[9,10] We believe that for further increases in patient survival and graft function to occur, major changes must be made in the approach to preventing graft rejection — changes that will specifically suppress the host response to the graft and that will not increase the recipient's susceptibility to infection.

In previous communications we have examined the effect of the presence or absence of cytotoxic antibodies to individuals other than the kidney donor,[31,32] the influence of other systemic diseases such as Fabry's,[12] the special problems in pediatric transplants,[33,34] the relationship of graft and patient survival to ALG dose[20] and multiple other factors.[35,36] The rehabilitation of our transplant patients has also been reported.[37] The majority of our patients with functioning grafts are employed or working as homemakers. Approximately 25 recipients have given birth to normal children and numerous male recipients have become fathers after transplantation. In our opinion, the quality of life after transplantation is superior to that offered by chronic hemodialysis.[37] For this reason, we recommend transplantation even in patient subgroups where risk factors indicate that the chances for survival are equivalent to those of chronic dialysis therapy. The acceptance of this approach by our patients is illustrated by the desire of most of them to undergo retransplantation if the primary graft is lost.

The psychological and sociological climate for transplantation in the state of Minnesota is particularly favorable. Even though transplants with related donors are the most successful, in some centers many more transplants are from cadaver donors than from relatives. In contrast, at the University of Minnesota 60 per cent of all first grafts have been from related donors. Numerous factors may contribute to this fact, but it is apparent that family commitment to helping the patient with chronic renal failure is particularly strong in Minnesota. When cadaver kidneys are used, it is usually because an ABO and HLA compatible donor does not exist within the family.

Although the use of antilymphocyte globulin, the high percentage of related donors and reliance on HLA typing for donor selection, have been cited as responsible for the good results with transplantation at the University of Minnesota, we think a major factor in this success has been the commitment of resources to patient care. Numerous physicians, including residents in training, are directly involved in patient care. In addition, a large number of nurses are an integral part of the transplant program. Our transplant ward is staffed like an intensive care unit. Two nurse clinicians are involved full time in managing the large outpatient population. These individuals maintain contact with the patient and monitor laboratory tests that are performed at least three times a week in the early transplant period, and thereafter at monthly intervals.

Another important aspect of the University of Minnesota Transplant Program has been the academic and clinical training of numerous physicians in transplantation surgery and medicine. Since January 1970, 17 surgeons have completed transplantation specialty training at the University (Table 6). Thirteen of these individuals are now directing, or are affiliated with, transplant units throughout the world, and another two will soon be assuming similar responsibilities. Two of these surgeons (Drs. Sutherland and Howard) are currently part of the University's transplantation staff. Ten pediatrics and medical nephrologists have been trained in transplantation and dialysis nephrology. Five of these physicians are now directing dialysis units.

Although the transplant training program has been primarily designed to allow the physicians involved to obtain the background and experience necessary to organize and direct a modern transplant unit, these individuals have also contributed enormously to our program, both in clinical care of the transplant recipients and in transplantation research. This fact is emphasized by their numerous contributions to the

TABLE 6

Surgeons Trained in Transplantation at University of Minnesota

Transplant Surgeon	Years at Minnesota	Present Location
Richard Weil	January 1970-June 1970	Denver, Colorado
Goran Lundgren	April 1970-December 1970	Stockholm, Sweden
David Kinne	January 1971-June 1971	New York, New York
Schrae LaPlante	July 1971-December 1971	Morgantown, West Virginia
Eduardo-Delpin Santiago	January 1971-June 1972	San Juan, Puerto Rico
J. Octavio Ruiz-Speare	April 1972-June 1972	Mexico City, Mexico
Clive O. Callendar	July 1971-June 1973	Washington, D.C.
Claude DeShazo	July 1972-June 1973	Seattle, Washington
Luca Rattazzi	July 1972-December 1973	Seattle, Washington
Peter Spanos	July 1973-July 1974	Thessaloniki, Greece
Robert Casali	September 1973-December 1974	Little Rock, Arkansas
Martin F. Mozes	July 1974-June 1975	Chicago, Illinois
David E.R. Sutherland	January 1975-December 1975	Minneapolis, Minnesota
Richard J. Howard	July 1975-June 1976	Minneapolis, Minnesota
John Buis	January 1976-December 1976	Melbourne, Australia
Georgio Merino	July 1976-July 1977	St. Louis, Missouri
George Kyriakides	July 1977-December 1977	Miami, Florida
Ramiro Garcia-Reyes	July 1977-June 1978	San Diego, California

transplantation literature — only a few of which are included in the bibliography of this paper.

Numerous institutions throughout the world have contributed to the advancement of transplantation to the forefront in the management of chronic renal failure. The University of Minnesota has contributed particularly to the use of antilymphocyte globulin as an immunosuppressant,[20] simplification of the technique of organ preservation,[19] and demonstration of the rehabilitation potential of patients after transplantation for systemic diseases such as diabetes.[9,10] We hope that similar contributions will result from our future transplant endeavors.

Acknowledgments

Many individuals not included as authors or in the bibliography have made major contributions to the transplant program at the University of Minnesota and have been involved with transplantation patient care and management. Special acknowledgment is due Justine Willmert, R.N., Transplant Nurse Coordinator since 1967, for her superb care of the patients and coordination of the details in inpatient and outpatient management; Lois Bartel, R.N., has assisted Miss Willmert in this task in recent years. The secretaries in the transplant office, Audrey Boyd and Julie Reardon have communicated with the transplantation patients and maintained patient records. Only a few of the physicians directly involved in patient care can be listed: Dr. Theodore Buselmeier, nephrologist and pioneer in the development of vascular shunts for dialysis; Drs. Frederick Goetz and Josa Barbosa, diabetologists in the Department of Medicine; Drs. John Harris and Robert Ramsay, Department of Ophthalmology; Dr. David Bradford, Department of Orthopedics; Dr. William Kennedy, Department of Neurology; Dr. Cedric Quick, Department of Otolaryngology. Surgeons and nephrologists that pioneered transplantation at the University of Minnesota are listed as the authors describing this early experience in reference 5. Leslie Olson has been principal preservation technician since 1970. Marvin Haymond, Principal Social Worker, and his associates, have solved many knotty problems with the transplant patients. The dialysis and transplant nurses, technicians, and residents who have cared for the patients are too numerous to name; their dedication and enormous contributions are deeply appreciated. The surgeons who have trained in transplantation at the University of Minnesota are listed in Table 6. Fellows who have received special training in transplantation and dialysis nephrology at the University of Minnesota include Drs. Gerald Ireland, Theodore Johnson, Barry Von Hartitzsch, Francisco Rodrigo, Thomas Davin, Robert Lynch, Elizabeth Hodson, Christa Feldhoff, and Alberto Rosa.

Recognition is also given to Richard Condie for his role in the production of antilymphoblast globulin used to treat the transplant patients. The undispensable contributions of Drs. Edmond Yunis and Leonard Greenberg and the entire tissue typing laboratory are also greatly appreciated.

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22.-37 May be secured from the authors.

Indo-Chinese Refugees

Cultural Aspects in Working with Lao Refugees

KAREN OLNESS, M.D.*

THE FOLLOWING vignettes relate to cultural considerations in health care delivery from three cultural settings.

. . . As chief resident, you are working on a pediatric service at the University Hospital. A 2-year-old Lao child is hospitalized for treatment of meningitis. Each morning you see knives sticking out between crib slats, and the nursing staff are up in arms. They remove the knives which are replaced within hours.

. . . You are working in a kwashiorkor clinic in Nairobi, having only recently arrived from the United States. A well nourished appearing mother comes in with twin boys, age two and a half years, who appear puffy, light haired, and listless. Baked enamel-like dermatoses are apparent on their arms and legs.

When you suggest milk supplements she says that these give diarrhea. When you suggest eggs she admits that she eats one a day but says they cause convulsions in young children. She says she gives them meat in large chunks but only to suck on which she gives to the dogs after the twins have finished their sucking. Furthermore, she was brought here by the village health assistant. She doesn't understand why "because it is normal for children to be this way around age two."

. . . You are observing as a well meaning WHO nurse serves milk (UNICEF supplies) to her Lao nursing students at 10 am. From your vantage point you see that the students accept the milk with characteristic bow and walk around the corner to pour the glass of milk onto the ground.

. . . An American Indian child is hospitalized for treatment of severe pneumonia in the life support unit of your hospital. He is critically ill. His family wants to bring medicine men and have a service in the L.S.U.

Discussion

The recent arrival of many refugees from Southeast Asia into clinics, hospitals and physicians' offices should have made us all aware of the cultural influences which always surround health care, even in situations in which the physician and patient speak the same native tongue and were raised in the same town. Perhaps a benefit from health care professionals coping with obvious cultural differences with the Southeast Asian arrivals is that it makes us more acutely aware of different realities than our own. Even in a fairly uniform culture the so-called social construction of reality may have varying interpretations among individuals.

Culture, cultural norms, and the individual social self all play a part in the way a reality is defined. The term social self is defined as the way an individual conceives or presents himself to others. It includes such aspects as whether or not the person accepts all or part of the culture or sub-culture he is in and how he projects that acceptance or rejection to those around him. The term "culture" is defined as a way of life for a group of people — how they work, how they relax, their values and prejudices, biases and the way they interact with one another. This involves ethical and moral principles of a given society — something we call cultural norms. Cultural norms are usually unwritten but nevertheless understood as the rules or principles of a culture. People are expected to abide by these rules or norms. When people violate these they are frowned upon, and sometimes ostracized by others. It is worthy of note that living outside cultural norms may have a very significant health impact.

When we work with the newly arrived refugees from Laos, we need to understand the cultural perspectives or cultural definitions of what is health, what is sickness, what is well being? One needs to analyze health problems at increasingly complex levels. For example, one might consider the problem of pertussis in an infant. At the immediate problem level one must deal with the acute disease and treat that. If one considers an approach to the problem at a second level, the logical progression would be to prevention. One might proceed to procure pertussis immunization for infants and children. At that point one may move upward to a third problem level which may be finding resources to purchase the vaccine, or to a fourth problem level which is that the villagers do not believe that it is safe, from a spiritual point of view to give immunizations to babies. One may find it fairly easy to cope with the problems at the first three levels. Coping with the cultural problem is clearly most difficult.

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Culture and Cultural Norms

This article will make comments about culture and cultural norms in Laos which are general comments, but not specific to any one tribal group. Laos has a frontier that touches Vietnam, China, Burma, Thailand and Cambodia. Although very long in form it is obviously a very distinct geographic unit. Its physical unity is masked by comparative regional diversity. It has the contrasts of sparsely populated table lands and more densely populated valleys. Dozens of tribal groups are represented in Laos.

It is important to know there are "royalty" groups in each tribe and, while not as rigid as the old caste system in India, many tribal people are very conscious of social states. Therefore, an interpreter from a "lower" level than the patient may not be acceptable. It is really impossible for the average Minnesota health care provider to get the social level information from the patients and interpreters.

The concept of helping others and who one helps is related to family, tribe, and class levels. For example, in Laos a western physician may prescribe certain IV antibiotics for a hospitalized child, assuming that Lao nurses will carry out the order. This is likely to be done if the child is of the same tribe or clan level as the nurse. Otherwise, implementation of the order is problematic.

Lao families, on the other hand, help their own extended family members far more than is generally true in western families.

If one becomes a benefactor to the ethnic Lao, according to tradition he or she is forever a benefactor. This means that the Lao recipient has no embarrassment in continuing to request and accept support from someone who has once been a benefactor. For example, if one saves the life of a drowning man, he is forever responsible for the care of that person. If one provides an artificial arm for an amputee, he is expected to provide whatever else the amputee may need.

Climate and Calendar

The way of life has traditionally been greatly affected by the climate. In June the approach of the rainy season signals time for the heaviest work in the rice fields to begin, and the majority of the Lao population are busy for months at a stretch in the rice fields. In general men and women share the work alike. When the harvest is in and the future assured, the dry season provides the time for many holidays.

The Lao calendar belongs to the Lunar Solar System and is based on a complex astronomical method which provides predictions which are very important to the Lao people. The predictions have traditionally affected behavior and expectations of the population related to their harvest, their families and communities.

The Baci

The Baci is the Lao ceremony par excellance. It is an expression of welcome which greets officials, travelers, and the Lao in their families. A Baci is celebrated to wish long life and good health to a newborn child, to a sick person on the way to recovery, to a traveler about to take a long journey and at weddings. The word "Baci" is commonly sukhuan. Sukhuan means calling and welcoming the soul, for it is believed that the soul is a roving nature and only too glad to leave the body. After a ceremony to call the soul, the participants in the ceremony tie cotton threads to the celebrant's wrist who in turn does the same to the person to whom the sukhuan is offered. Each participant receives a lucky thread. It is important to note that if baci threads are seen on the wrists of patients they should not be cut. In general they remain on wrists until they fall off.

Pregnant Women and Taboos

Traditionally, many taboos are placed on a pregnant woman. These include foods such as larva from bees, tamerinds, and bananas containing seeds. She must not step over the head rope of a horse or an ox lest the child be greedy, nor sit on the upper step of stairs as it might delay the birth. If she wants to dry her skirts in the sun she must see that the bottom is placed in the direction of the sun so that the head of the child will come out first. Labor rituals are complex with many family members and the witch doctor or a man — midwife is involved in facilitating the delivery. Following the delivery there is a Baci ceremony for the baby and the mother. Following the delivery, ethnic Lao women are admonished to sit by a fire, even in the hot season, for several weeks. Their diet is restricted to tea and chicken broth during the postpartum period.

Marriage and Death Rites

Marriage rites and death rites are complex. Among all the different causes of death the natural one from disease confers the right to great privileges. Persons who have suffered a violent death will not be cremated but buried without delay. According to religion and customs their remains should not be kept at home for more than 24 hours. Because to die in Laos is to enter nirvana, it is a happy event. Whatever the specific meanings, nirvana for Lao people is generally a place for enjoyment where all desires are fulfilled. In general, following a natural death there are seven days and nights in which the home is the center of gatherings. After seven days the coffin is brought to a hut erected for the purpose in a corner of a field belonging to the family. The style of the coffin varies in different areas. Cremation dates are generally picked for the dry season. Cremation ceremonies last not less than six days and six nights and are often filled with processions and religious services which alternate with fireworks and night games and feasts. The feast reaches a climax at the time of the actual cremation.

Harvest Festival

One of the most happy festivals in Laos is that of the boun Khoun Khao (the harvest festival). It occurs in December or January and is held by a farmer who feels himself satisfied with the harvest. The harvest master will consult neighbors to fix an auspicious day for the boun, and the presence of monks from the wat are requested at the harvest site. Music is provided by performers on the khene, a reed instrument. Through the night a kind of court of love develops with a dialogue between young men and women. This goes on through the night with much so called oratorical jousting. Molams are brought to entertain older people. The Molams serve as wandering story tellers and news relayers and are highly regarded in Lao villages.

Fishing

In addition to rice farming, one of the principle occupations in Laos is fishing. Most Lao live in proximity to a river bank and fishing is a family affair. The Lao language is replete with many complex words for aspects of fishing which have no equals in English language. It is important that Laos in Minnesota often go fishing in the Mississippi and it is unlikely that they will follow prescribed rules with respect to the amount of fish eaten, which one can safely eat in a week from our rivers. Parts of fish are often used in the local pharmocopia. For example, the spiny dorsal fin of one fish is used in cases of mumps and sore throats.

Names

Names of Laos are often very confusing to Westerners. Before 1944 there were no such things as surnames. The names that people were given in birth were very few. There was a custom which helped them to avoid mixing up two people whose names were the same. These were title names for people of high estate or low estate. In 1944 the family surname was determined by the name of the oldest male member of the family and the direct line of ascent who was alive on January 1, 1944. In private life, people still do, as a rule, hail each other by their old first names.

Code of Behavior

Aspects of the Lao code of good behavior which are relevant to those who are involved in the health care are as follows: it is a real act of discourtesy to touch someone's head. And, if the head must be touched in examination, it is a good idea to ask permission to do so. A sign of bad breeding is to point out an object with one's foot. Crossing the legs is unheard of, and the person toward whom the toe is pointing will perceive himself insulted. It is unseemly to knock at doors when one is arriving. Correct Lao time is an hour late for the specified time. If you arrive at 9:00 p.m. when you were invited at 8:00 p.m. you are keeping correct Lao time.

Taboos

Some taboos are: it is forbidden to cut hair on Wednesday, because it is the day in which the Buddha had his hair cut. For the same reason it is forbidden to wash one's hair on Thursday. It is forbidden to eat in a reclining position lest one becomes a serpent. It is forbidden to eat liver and gizzard of a chicken, for that would deprive us of our intelligence. It is forbidden for an infant to eat eggs because that would cause him to have no teeth.

Lao Food

With respect to food, rice forms the basis of people's every day fare. Many of the Lao people prefer to eat sticky rice with their hands. They prepare a great deal of meat and fish in raw form adding certain spices. Khaopoun is a favorite dish of foreigners. This is made of rice vermicelli to which a variety of chopped raw vegetables are added in addition to meat or fish and cooked in coconut milk. In general Lao regard fruits as play food. They do not eat them routinely and, in fact, do not feel they have had an adequate meal unless it includes rice. The majority of Lao people traditionally have been Buddhists, and many Lao spend a portion of their life as monks. One sees the monks making rounds in the morning for food donations from villagers. In Laos, however, animistic beliefs are also incorporated in to Buddhism. A belief in spirits explains for example the knives that will be placed between crib slats in a child's bed in the hospital.

Medicine

Traditional medicine in Laos may be provided by the quack, the magician, or the witch doctor. In order for a family to know who is to be called, an egg is taken and rolled lightly and slowly over the body of the patient, particularly over the aching spot. After a few minutes, efforts are made to stand the egg on a board. When the egg stands somewhat appropriately the operator taps the board. The shell of the egg is then broken and, on the basis of the embryo, a decision is made whether the quack, the magician or the witch doctor will be called. The so called quack lights candles, recites prayers, and recites magical formulas and concocts a potion from various roots, branches, bones, horns, etc. The ceremony of the magician includes a large tray which has specific flowers, fruits, eggs, and other objects prescribed by the magician. The magician conducts discussions to find what angered the evil spirit and then has a ceremony to remove the evil spirit. Many people believe that sorcerers have the power to insert disease and death into patients. The witch doctor passes a lighted candle over the body until he finds the foreign matter inserted by the sorcerer. He then attempts to cause the patient to vomit out the foreign matter.

American Physicians

It is important to remember that the Lao refugees, like others from Southeast Asia have been wrenched from the cultural traditions and mores which have been briefly described to a culture which is very foreign to them. As we would, in their culture, they tend to hang on to their beliefs and traditions. Physicians here can be certain that there are magicians, witch doctors, and herbal potions with the Lao refugees. To further complicate matters, many have assortments of antibiotics which may be purchased by anyone in some pharmacies in the Far East. A favorite is chloramphemicol which is dispensed to many children at the first sign of a fever. Obviously, one of the great problems for pediatricians is to examine a child without touching the head or to remember to apologize before examining the child's head. It is important to ask the family's permission before putting IV lines into a scalp vein. A physician or nurse may inadvertently insult a Lao patient by crossing his or her legs and pointing a toe at the patient. These may seem like small things and yet, of course, they are very important, most important to the Lao adults. Their children will rapidly assimilate into our culture. Our culture will also absorb a bit of Lao traditions and, indeed, we will be a richer country for it.

Accredited by AMA and LCCME

The continuing medical education program of Riverview Hospital Association in Crookston was accredited by the MMA Medical Education Subcommittee on Accreditation at its last meeting. Continued accreditation was granted to North Memorial Hospital, Minneapolis following resurvey of its program. The Minnesota Medical Association acts as an accreditation agency in continuing medical education for the American Medical Association and for the Liaison Committee on Continuing Medical Education. For Further information submit written request to: Donald Nollet, M.D., Subcommittee on Accreditation, Minnesota Medical Association, Suite 900 — 101 E. Fifth Street, St. Paul, Minnesota 55101.

Cover Photo

"Two Tall Ones in East Africa"

View of Mt. Kilimanjaro in Masai country of Southern Kenya, East Africa. This 19,000 foot peak dominates the scenery of Amboseli Game Park where large numbers of wild animals live in their natural habitat.

Dr. Oliver Peterson is an Obstetrician and Gynecologist in Minneapolis and spent February and March 1978 working in an African hospital.

Rheumatology Corner

D-Penicillamine in the Treatment of Rheumatoid Arthritis

CHARLES H. McKENNA, M.D. *

D-PENICILLAMINE WAS first used in the treatment of rheumatoid arthritis (RA) by Jaffe in 1965. Although several uncontrolled studies reported its efficacy, this was not clearly established until the Multicenter Trial Group's report in 1973.[1] This drug has recently been approved by the Federal Drug Administration for use in rheumatoid arthritis.

No clinical or laboratory predictors of efficacy exist which permit a choice between the use of gold, Penicillamine, and the antimalarial drugs in the treatment of RA. Accordingly, unless a previous trial of one of these agents has ended in failure or unless perhaps the patient has active peptic ulcer disease, the choice between them is arbitrary. Some authorities believe that the frequency of benefit is greater with Penicillamine and gold than with antimalarials.

Penicillamine is available in 125 and 250 mg tablets. A typical protocol of administration would be 250 mg of the drug daily for a month followed by 500 mg daily for a month followed by 750 mg per day. Higher dosages can be employed at the risk of a higher incidence of toxicity. A decision to use higher dosages must be balanced against the risks and advantages of alternative forms of drug treatment. Not more than 500 mg of the drug should be given in a single dose but otherwise no special advantage is gained by giving multiple divided daily dosages. Should minor toxicity or a therapeutic response occur, the dosage of the drug is reduced to the lowest level consistent with maintenance of the therapeutic response or the highest dose consistent with remission of toxicity. In such maneuvers, the use of the 125 mg tablet permits more precise dose adjustment. If a therapeutic response occurs, clinical improvement is not usually seen for three to four months.

Females at risk of pregnancy should employ effective contraception when treated with Penicillamine, and the drug should be discontinued if they become pregnant. Penicillamine is discontinued if drug fever occurring within two to three weeks of initiation of treatment occurs. It should not be resumed. Generalized pruritic maculopapular drug eruptions not associated with fever usually remit after the drug is discontinued and often do not reoccur when a lower dosage of the drug is reinstituted. Intensely pruritic or pemphigoid drug eruptions require permanent termination of Penicillamine treatment. Hypogeusia usually remits even if treatment is continued. Development of bone marrow suppression, nephropathy, oral ulceration, or drug induced systemic lupus erythematosus call for at least temporary and often permanent discontinuation of treatment.

Bone marrow suppression and nephropathy are side effects of Penicillamine which will be detected by laboratory testing for toxicity before the patient has developed symptoms of these toxic responses.

Weekly determinations of hemoglobin, white blood cell count, and platelet count are done for three months and monthly thereafter. Urinalyses are carried out monthly and if a significant change in the semi-quantitative protein excretion occurs, a quantitative determination is done and the drug is discontinued if necessary.

Space does not permit a full discussion of this agent. Physicians employing it must familiarize themselves with the usual prescribing information and literature before employing the drug.

---

*Assistant Professor, Mayo Medical School, Rochester, Minnesota.

Reference

1. Multicenter Trial Group Lancet II, 75, 1973.

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Anderson, C. F. Co. . . . 854
Burroughs-Wellcome Co. . . . 878
Classified Advertising . . . 894
First Bank Minneapolis . . . 857
Lilly, Eli & Co. . . . 852
Marquette National Bank . . . Cover 2
Mead Johnson Pharmaceutical Division . . . 887, 888
Medcalf Orthopedic Appliance Company . . . 900
Medical Protective Company . . . 876
Merck Sharp Dohme . . . 854, 858, 859, 860
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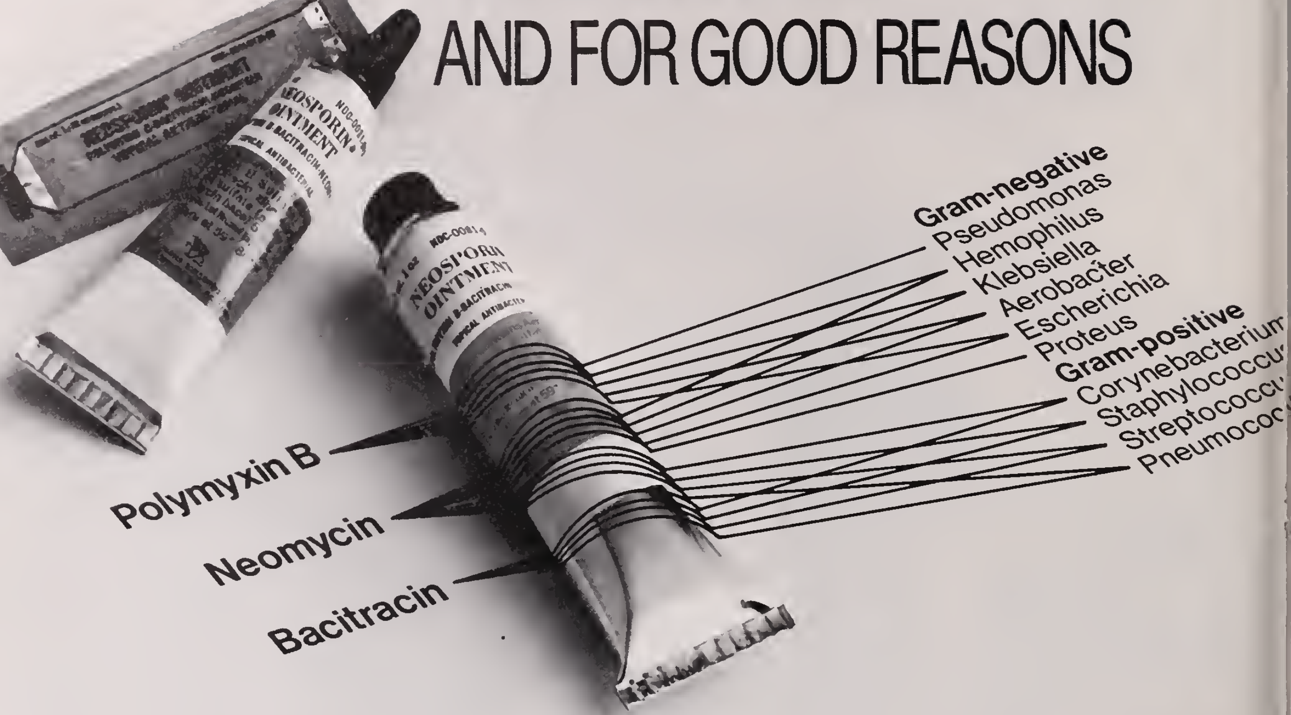

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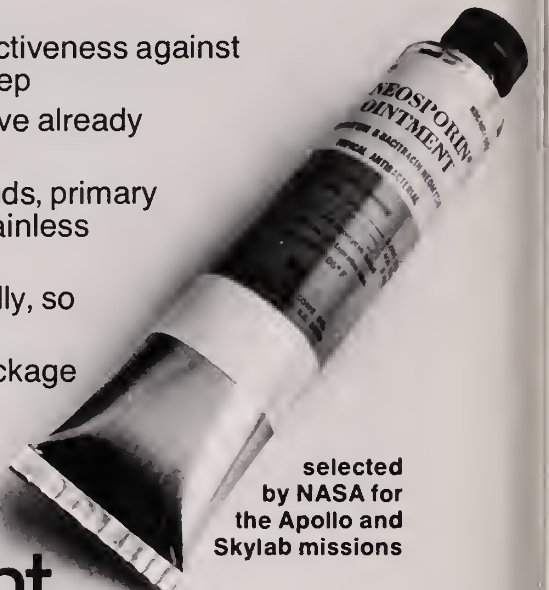

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Special Article

Surgery's Reawakening
(1937-77)

OWEN H. WANGENSTEEN, M.D.*

MANY OF YOU, I know, are now plotting your future course of action. You must soon make the important decision of whether to remain on the professional treadmill or to accept superannuation. Those of you in the academic arena are aware that many institutions, including the University of Minnesota, regard retirement as a reward of idleness, a frosting on the cake for prior years of devoted service, without providing adequate provision for support of retirees. You have just witnessed the performance of a group of your former teachers who have chosen to remain in harness on the periphery of their former pursuits. You have provided each of us with more than a homeopathic dose of honor in inviting us to share this occasion with you. It is good to be remembered. I was retired less than a week from my duties in the Department of Surgery when I ceased to receive mail. On inquiry, I learned my letters had been returned to the senders with the advice, "There is no longer anyone here of that name." Lord Russell Brock, one of Britain's most distinguished surgeons told Sally and me at dinner a year ago in London, he had been excluded from his hospital wards at Guy's Hospital shortly after retirement by a young nurse to whom the name of the distinguished visitor was unknown. Retirees are of the past, which has little or no meaning for many. The future of all institutions rightfully is in the hands of the oncoming generation.

A few years of truancy without daily obligations may appear enticing to some of you. However, do take note of the satisfactions manifest in the attitudes of your prior teachers who obviously have found inspiration and stimulation in a variant of earlier commitments. I am under deep obligation to this Great University and its Medical School having early acquired a nice opportunity when I ill deserved it. And now that I am well past the biblical "three score years and ten" I am fortunate in the privilege of being permitted to continue my labors.

In your Class there are a large number of Minnesota graduates whose work and accomplishments have added lustre and increased status to the Institutions you serve. Our Medical School is proud of you. When my Class of 1922-23 had been out 25 years, 71 of its 73 graduates were alive. A Committee of the Class was appointed to select a proper memorial. Recalling the modest accommodations in our medical library, a single room on the ground floor of Millard Hall, we decided on a Fund to purchase books for the Library. A fund of something less than $5,000 was provided, two-thirds of the graduates contributing. On our 40th anniversary paralleling today's celebration more than a third of the graduates were no longer among the living. A Committee of that Class decided to reduplicate in kind the earlier gift at 25 years, a recommendation approved of when the Class convened. This time somewhat in excess of $10,000 was donated for book purchases for the Library. Our Biomedical Library, meanwhile, as you know, has made great strides through the generosity of several affluent community friends and patients. The art and philosophy of giving is a more acceptable thesis today than it was before World War II. The entire world has come to appreciate its dependency upon research for advance in all disciplines. Your Class, I know, is seriously considering what activity in the medical school it will support. We are all under deep obligation to the University and its Medical School for the nice opportunities it provided us. Will some graduating class presently be willing to undertake the task of endowing a professorship, of which our School stands in great need?

With the help of grateful generous patients, it should not prove an unrealistic objective. During his productive Deanship at Harvard Medical School, George Berry provided 60 endowed professorships. Physicians as a group are not a moneyed class. However, they are in a unique position to persuade affluent appreciative patients to share their plenitude with worthy public institutions. Frugal living and public philanthropy are qualities that contribute significantly in building great schools, a practice deserving of emulation in our area. On the 40th anniversary of my medical school class in 1962, an attractive, young-appearing, articulate, modishly dressed woman, the wife of a very successful specialist-husband asked: "We support our State University's Medical School through taxes, is that not enough?"

---

*Regents' Professor, Department of Surgery, University of Minnesota, Minneapolis. Presented at the 40th Reunion of the Medical Class of 1937, May 23, 1977.

Being the spokesman for our Class Committee, I replied, "No not half enough; we who have had unique opportunities owe a debt of great gratitude to our alma mater, our foster-mother, best recognized by providing her the privilege to accord succeeding generations of medical students even greater opportunities." I fear she was not convinced. Example provides the best stimulus to generous giving. What Paul Dwan, Jay Phillips, and other generous citizens in this area have done on this score is deserving of emulation by all of us.

Management of Cellulitic Infections

Your graduation here in 1937 marks the beginning of the availability of sulfanilamide, an agent that proved very effective in the control of streptococcal cellulitic infections. Some of you will recall that in your early years here, the surgeon in his wrestle with infections was essentially a pus evacuator. When he tried to do more, he usually did harm. Some of my surgical teachers returning from World War I were imbued with the idea that implantation of an antiseptic into infected wounds would stop its ravages, following out Lister's thesis of 1867 for which purpose he had used carbolic acid. Carrell and Dakin in World War I employed a hypochlorite, which agent Semmelweis at the Vienna Allgemeines Krankenhaus (1847) had employed so effectively as prophylaxis more than six decades earlier. Let me tell you of a young school teacher, Julia Schaub of the St. Cloud area, aged 23, admitted to our hospital in January 1934 for a septic phlegmon of the left thigh and leg resulting from an explosion in the woodstove in her country school house. One of the lids of the stove struck her left thigh with great force, causing a compound fracture of the femur. An experienced World War I surgeon made multiple incisions in the thigh and leg in two operative sessions. Continuous irrigation of the resultant wounds by the Carrel-Dakin technique had not the slightest restraining influence upon the infection. A senior orthopedic surgeon, also with World War I experience, counseled amputation at the hip joint, which advice the patient rejected. This surgeon, with the assistance of Melville Manson, senior surgical resident who came from Worthington, then applied a double leg spica body plaster cast extending from the toes to the axillary folds. Its effect upon pain, fever, and the general course of the patient was immediate and dramatic, the patient making a satisfactory recovery from what appeared to have been a hopeless situation. It is for similar cellulitic streptococcal infections that sulfanilamides and antibiotics have had such a significant impact.

Nineteenth and Twentieth Century Innovations

Chemotherapy and antibodies in the twentieth century have extended the surgeons' reach considerably in dealing with infection though the problem is far from having been completely solved. Two Cinderellas of the Profession provided two of the great medical discoveries of the nineteenth century. Dentistry gave us anesthesia, contributions of William T. G. Morton (1846) and Horace Wells (1844); prophylactic surgical antisepsis came as a gift from obstetrics in 1847 at the hands of Ignacz Semmelweis, a Hungarian physician in residence at the Vienna Allgemeines Krankenhaus. Certainly, medicine's greatest therapeutic advance came in the final quarter of the nineteenth century as a product of the new science of microbiology, creating elective surgery. It was the work of Robert Koch (1876-78) that definitely established the pathogenicity of bacteria, a thesis dating back to Fracastoro (1546), a contemporary of Vesalius and Ambroise Paré who wrote of *seminaria* (germs) as a frequent source of infection by contact.

The miracle drugs of insulin, vitamin B_{12}, cortisone, and others of this century have created new life for many. The work of the Live-Stock Sanitary Board (1910-35) eliminated the threat of bovine tuberculosis, as did streptomycin and other specific agents for human tuberculosis a decade later. Poliomyelitis has been conquered. These achievements, the products of research eliminated the need for surgery, a great gain for medicine. Surgery's most important contribution to medicine in this century has been intracardiac surgery, in which accomplishment Minnesota's Department of Surgery was privileged to have a hand. When my great friend, Maurice Visscher returned to the University in 1936, we began at once a weekly physiology-surgical seminar, discussing the solution of difficult and recurrent surgical problems. The first important windfall thereof was the mass spectrograph provided by the eminent Minnesota physicist, Alfred Nier, a device which provided anesthesiologists with instantaneous assessment of the concentration of inhaled anesthetic gases; today a small portable apparatus has supplanted the large original device and is regularly used in hospitals throughout the world.

In the mid-1930s, intracardiac surgery loomed as a possibility through the work of John Gibbon, a Philadelphian who had devised a pump oxygenator to substitute for the heart and lungs during cardiac standstill. As World War II came to an end, I was persuaded that resolution of this challenging problem lay in training talented young surgeons in the intricacies of the circulation. Visscher, one of Ernest Starling's last pupils agreed. By the early 1950s we were ready. F. John Lewis, who emanated from Tracy, Minnesota did the first successful repair of an interatrial septal defect in a child aged five under hypothermia September 2, 1952. Clarence Dennis made two unsuccessful attempts to correct interventricular defects with a pump oxygenator of the Gibbon model. Then C. Walton Lillehei and his collaborators used successively and successfully the cross-circulation technique, employing a compatible donor; and later the transfusion principle for small infants. Then came the DeWall oxygenator. DeWall, who emanated from Appleton, Minnesota, was in practice in Anoka and had decided to become a surgeon. His academic record was such that he could not be registered in the Graduate School, where upon I engaged him as a laboratory Diener at a higher level of pay. When later I wanted to enlist young, well motivated men in our program with unsatisfactory records of medical school performance, all that was necessary to say to Dean Blegen was "Remember DeWall." C. Walton Lillehei emerged as the Leader of that great band of intracardiac surgeons which included many other names familiar to all of you, among others Richard Varco, Herbert Warden, Morley Cohen, Al Merendino, Vincent Gott, Norman Shumway, Christiaan Barnard, Aldo Castaneda, Ernesto Molina and many others. In the achievement, I merely occupied the role of water-boy and side-line cheer leader.

Early Events Marking Surgery's Acceptance

Accomplishment is the Hallmark of professional and social acceptance. Over the centuries there have been a few remarkable innovations and events that lent surgery increased professional status and public recognition. In 1536 the barber-surgeon, Ambroise Paré substituted turpentine, oil of roses, and egg yolk for the conventional hot, scalding "oyle of Elders of de Vigo," in the treatment of battle wounds. When Charles François Felix (1686) cured Louis XIV's chronic fistula-in-ano by operation, surgery in France achieved a spirited public awakening, appreciation and Royal favor that carried through for more than half a century, leading to the creation of five chairs of surgery at St. Come under Louis XV (1724), and L'Academie Royale de Chirurgie in 1731.

James Lind of the Haslar Hospital in Portsmouth took 12 sailors ill with scurvy to sea in the Mediterranean in 1747 performing the first controlled experiment in medical annals, proving that two oranges and a lemon added daily to a basic diet cured sailors of scurvy within a week.

John Hunter's pupil, Edward Jenner (1798) converted the tradition of milkmaid's immunity to smallpox, as a sequel of having contracted cowpox, to scientific reality.

With the advent of elective surgery (ca 1885), saw-dust covered floors of the operating room, reminiscent of the slaughter-house, gave way to marble floors and walls, and teakwood seats for students and spectators throughout Britain.[2]

Advance through research is a discontinuous process. Today, the Research Center approach employing the keenest minds of all medical disciplines dominates the scene. There are, however, long periods of lull when progress comes to a halt, awaiting new innovations; a period during which assessment and scrutiny of all existing information can prove very helpful: witness what happened in Cesarean Section and the maternal mortality of childbirth. This device obviously can be applied to a number of situations such as the mortality of appendicitis.

Surgery had a reawakening in America after World War II with considerable improvement of our professional and public image. Let it not be tarnished by greed for money. Nothing in the world is so easy to get accustomed to as money, and how sad! Shared opportunity is the finest paymaster in our worthy profession.

Acceptance of Primacy of Teaching by Senior Professors

In conclusion, I would like to point out that our teachers in earlier decades of this century took their primary commitment to teaching seriously, far more so than do many senior faculty members today. The Hippocratic Oath has been avowed by physicians entering the profession for 20 centuries. Since Plato, a contemporary of Hippocrates, established the School of Academe, it has frequently been said that the effective teacher affects eternity. I would like to propose a Teacher's Oath in which a senior member of all medical faculties, at the beginning of each school year, declares before the school's entire student body, that the faculty recognizes their responsibility as teacher as one of their primary functions. Students, I feel certain, would appreciate such an innovation.

The best measure of a teacher's success is his intellectual progeny. Should not professors strive to provide their proteges with an opportunity of equal quality to what they have enjoyed? Such is the very source and strength of how great Schools develop in which the progeny surpass their masters. Bernhard Langenbeck at the University of Berlin for 35 professorial years (1847-82); Theodor Billroth for 27 years at the University of Vienna (1867-1894) and William Halsted at The Hopkins for 33 years (1889-1922), all used this technique to great advantage in replicating their kind and developing enduring schools of surgery that perpetuate the influence of the originator.[1] Sharing is a magic word and shared opportunity is the finest paymaster of academicians.

One of my concerns for current-day medical graduates is the great emphasis they attach to laboratory data, an attitude obviously conveyed by their teachers. In your day and mine, the seasoned physician lent considerable more importance to the history and physical examination. In emergency situations, the young, well-trained house-officer frequently orders a large number of unnecessary x-ray procedures and other laboratory data, not directly related to the problem at hand. Is fear of the threat of malpractice responsible for this common practice? John Simon, distinguished London surgeon-sanitarian in his report to the Privy Council in 1854 (p. xxv) wrote that trial by jury of alleged malpractice is "subornation and prostitution of justice." His advice was that such charges be heard by a judge who would assemble a few recognized experts to provide testimony and judgments in the matter. It is, indeed, high time that in such instances current trial by jury be abandoned throughout our country.

Some of your erstwhile teachers have appreciated the opportunity of sharing the afternoon with you. That the Class of 1937 wanted to catch a glimpse of their old teachers is a source of great satisfaction to us. In resolving the last segment of the best known of the Hippocratic aphorisms, "Life is short, the art long and judgment difficult," may you all make that decision which will bring you and your families greatest satisfaction and happiness.

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1 Wangensteen, Owen H Some post-Renaissance systems and schools of surgical training Proceedings of the XXIII International Congress of the History of Medicine (2-9 September, 1972), volume 2, London Wellcome Institute, 1974, pp 1017-23

2. Wangensteen, O H and Wangensteen, SD The Rise of Surgery, its emergence from an empiric craft to a scientific discipline In Press with the University of Minnesota Press, 1978.

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History

Thomas E. Keys

Medical Librarian, Historian, Scholar, and Author—Extraordinarius

JACK D. KEY, M.S., M.A.*

THOMAS KEYS graduated from Beloit College, Beloit, Wisconsin, in 1931, with the degree of Bachelor of Arts and received his M.A. degree from the Graduate Library School of the University of Chicago in 1934. He was library assistant at the Newberry Library in Chicago in 1931 and 1932. He attended the University of Chicago as a Carnegie Fellow in the Graduate Library School in the fall of 1932 and held a graduate assistantship in 1933.

Keys came to Rochester, Minnesota, in 1934, as assistant librarian of the Mayo Clinic. He was appointed reference librarian in 1935, a post he held until 1942, when he was granted a leave of absence to become librarian in charge of rare books of the Army Medical Library in Cleveland, Ohio. He discharged the duties of this post with distinction and was awarded the Army Commendation Ribbon by the Surgeon General of the Army. He was promoted through the grades from first lieutenant to lieutenant colonel.

Returning to the Mayo Clinic as Librarian in 1946, Keys continued in that capacity until April 1, 1970, when he became senior library consultant. He retired in December of 1972. He was named assistant professor of the history of medicine of the Mayo Graduate School of Medicine in 1957, was advanced to associate professor in 1963, and became professor in 1969. He was a member of the Board of Regents of the National Library of Medicine from 1959 to 1962.

During his tenure as Mayo Clinic Librarian, the holdings of the Mayo Clinic Library were greatly expanded; during World War II, for instance, it was recognized in Washington D.C. and elsewhere that the Mayo Clinic's collection of Russian periodical medical literature was the largest in the United States. The impressive acquisitions of rare books in the Mayo Clinic Library resulted almost entirely from the unceasing efforts of Dr. Keys in that endeavor.

Dr. Keys (Figure) revived and virtually single-handedly stimulated an abiding interest in medical history which has persisted at the Mayo Clinic and Mayo Foundation, and he is the author or co-author of a number of volumes on the history of medicine. On April 17, 1972, he was awarded the honorary degree of Doctor of Science by Beloit College, the citation reading in part, "Your lifelong commitment to excellence and innovation in your chosen career has helped in large part to create one of the world's greatest medical libraries and has won for you national distinction in the library profession."

Persistently active in professional association ac-

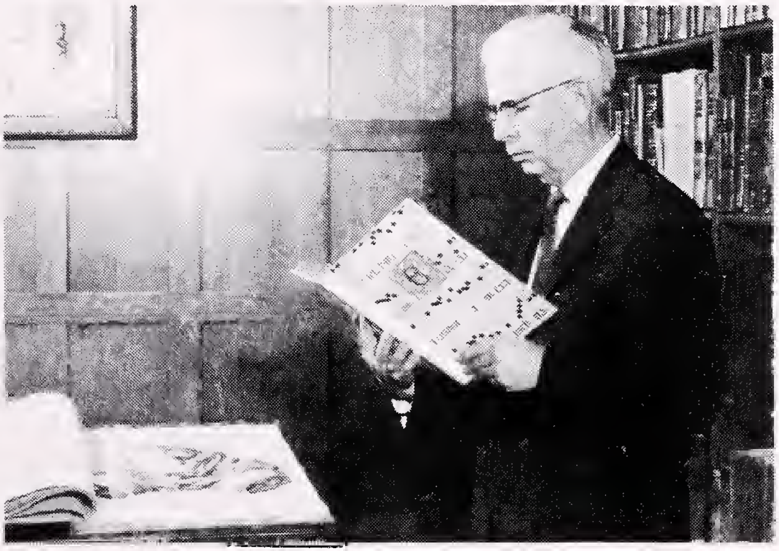

Figure — Thomas E. Keys.

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*Librarian, Mayo Clinic, Rochester, Minnesota

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tivities, Dr. Keys served as President of the Medical Library Association (1957-1958) and in 1966 was the recipient of the Marcia Noyes Award for "Outstanding Achievement in Medical Librarianship" (the highest award a medical librarian can receive from his professional colleagues). He is also a member of the American Association for the History of Medicine, International Society for the History of Medicine, Special Libraries Association, Sigma Xi, Pi Kappa Alpha, Beta Phi Mu, Phi Beta Kappa, Charter Member of the American Osler Society, honorary member of the American Society of Anesthesiologists, and a corresponding member of the Swedish Medical Association, Section on Medical History.

Dr. Keys was editor of the *Bulletin of the Medical Library Association,* 1942-1945; served on the editorial board of Blakiston's *New Gould Medical Dictionary,* published in 1949; was compiler of *Cardiac Classics* (1941, in association with Dr. F. A. Willius); was editor of the two-volume *Foundations in Anesthesiology* (1965, with Dr. A. Faulconer, Jr.); and was author of several books including *The Development of Anesthesia* (1943), *The History of Surgical Anesthesia* (1945), and *Applied Medical Library Practice* (1958). To date, there are a total of 152 citations in his bibliography of publications. He has also lectured extensively in the United States, the Far East, and Europe.

A colleague[1] said about Keys in 1957, which is equally true today,

> . . . to the present, his footsteps have not deviated from the primrose path of librarianship. With like restraint, and good fortune, he has needed but two libraries . . . as theatres of operation. If they happened to be good ones, he has made them better.

Tom Keys has given service of mind and heart to the Mayo Clinic Library, exemplified professional achievement with worthy accomplishments, and demonstrated confidence in the professional abilities of himself and his associates. To really appreciate some of the diverse contributions of this man, one must sample, then digest, from the potpourri of his published delights. Representative annotated examples are presented as follows:

The Colonial Library and the Development of Sectional Differences in the American Colonies. Libr. Q. 8:373-390, July, 1938.

In the colonial era, geographic barriers and differences in religion, nationality, and traditions helped to create three distinct groups in the American colonies. The purpose of this study was to discuss the development of sectional differences as represented in the private and semiprivate colonial libraries. Each group had its own personality, and the striking differences revealed in the libraries of the North and the South, for example, show the beginnings of the disastrous sectional cleavage that continued for the next hundred years.

This article has a good bibliography of catalogs and inventories of the individual libraries for the period.

The Medical Library — A Laboratory for the Literary Physician. Minn. Med. 22:633-636, Sept., 1939.

A library is complicated. To have a proper understanding of how to make the best use of the collections, one should be exposed to studies in medical bibliography and techniques. Library patrons should have a clear understanding as to what constitutes a library and what they can expect in respect to service or help in answer to their many problems. The library might be thought of as a laboratory, as it is indeed a workshop for the literary physician.

The Medical History of George Washington (1732-1799) I.-III. Proc. Staff Meet. Mayo Clin. 17:92-96, Feb. 11; 107-112, Feb. 18; 116-121, Feb. 25, 1942. (Written with Dr. F. A. Willius.)

This is one of the best accounts to be found on medicine and George Washington. His health and illnesses are discussed in detail in a three-part series. It was mentioned in the magazine *Time*.

The Plague in Literature. Bull. Med. Libr. Assoc. 32:35-56, Jan., 1944.

Very moving descriptions by "men of letters" of a dread disease are recounted in this excellent article on the plague. One effective narrator of the plague and its ghastliness was Boccaccio, who described the plague at Florence (1348). Another was Chaucer in his *Canterbury Tales*. Still another was Ben Jonson in his famous play, *The Alchemist*. Shakespeare too used the language of the plague on many occasions but did not seem to use it in the development of any of his plots. Daniel Defoe was still another author who used the Black Death as a theme in his many works. Descriptions of the "Pestilence" are many and they have provided much vivid and frightful ammunition for the pens of the literalists.

A Stained Glass Window on the History of Medicine. (Foreword by D. C. Balfour, M.D. and Description of the Window by T. E. Keys.) Bull. Med. Libr. Assoc. 32:488-495, Oct., 1944.

In September 1938, Dr. and Mrs. W. J. Mayo dedicated their beautiful home to the Mayo Foundation. It was their hope that the Foundation House, the name given to their former home, would be a meeting place where men of medicine would exchange ideas for the good of mankind. So that the donors' ideas could be carried out, certain changes were necessary. The great hall on the third floor was named Balfour Hall, in honor of Dr. Donald C. Balfour, and modified to accommodate meetings. Fine wooden paneling surrounded the hall and incorporated shields carved in wood of the renowned medical schools of the world. On the south wall hung a portrait of Dr. Balfour by Ivan O'Linsky of New York. On the west wall was a portrait of the Doctors Mayo by Johannson, a gift of the Alumni Association.

It became obvious that the east window was particularly well adapted to stained glass and that this window could be made to harmonize with the historical motif suggested in part by the shields and in part by the general character of the room. A committee was formed to study this problem. After many sessions, a stained glass window was designed and installed. The window as designed covers 2,500 years of medicine, giving emphasis to the basis of medical progress through the centuries, and it correlates the history of medical practice, medical education, and medical research. There are four panels in each of the three columns, and each horizontal level of panels depicts one particular era of medicine. In each panel, outstanding men, institutions, and events are representative of the great contributions made during that era.

Dr. Simon Baruch and His Fight for Free Public Baths. Arch. Phys. Med. 26:549-557, Sept., 1945. (Written with Dr. F. H. Krusen.)

This is an interesting story of a subject and problem we of the 1970s take much for granted. Dr. Simon Baruch, often called "the apostle of bathing," was the leading exponent of hydrotherapy in America from 1889 to his death in 1921. His mission, which was highly successful, was to create free public shower baths for the masses in order to abolish uncleanliness, an ever-present disease-producing factor. He suggested rain water, for river baths, he believed, were not fit for cleansing purposes. (He defined Manhattan Island as "a body of land surrounded by sewage.")

The Reference Function of a Medical Library. J. Lancet 72:565-566, 589, Dec., 1952.

Basically, the reference function of a medical library is in the interpretation of its resources: to make the materials easily accessible, teach the use of the library, maintain an up-to-date collection, compile bibliographies and special-use lists of materials, assist with translations, teach with the use of exhibits, and perpetuate an appreciation for medicine through its history.

The "Salmonia" of Sir Humphry Davy. Bull. Med. Libr. Assoc. 44:431-442, Oct., 1956.

Sir Humphry Davy with his book *Salmonia* (1828) hoped to do for the fly fisherman what Izaak Walton did for the bait fisherman with *The Compleat Angler*. In December of 1828 Sir Walter Scott honored Davy's *Salmonia* with a most favorable review 32 pages long.

Changing Concepts in Library Services. Bull. Med. Libr. Assoc. 45:5-13, Jan., 1957.

Traditional library service concepts are contrasted with library "futurism." The era of the application of scientific management of libraries is predicted and automation is said to promise "the solution to problems heretofore neglected because of their immensity."

The Atlases of Ophthalmoscopy: A Bibliography, 1850-1960. Am. J. Ophthalmol. 49:881-894, May, 1960. (Written with Dr. C. W. Rucker.)

An interesting and useful annotated bibliography is provided of ophthalmoscopy atlases from the Helmholtz *Beschreibung eines Augen-Spiegels* . . . of 1851 to 1960. Louis Pasteur once said, "In the field of observation, chance favors only the mind which is prepared." In medicine, it seems, there is nothing more true. Helmholtz not only invented his *Augen-Spiegel* but recognized its importance and applications. He had a receptive mind and won the credit for his accomplishment. In contrast, Charles Babbage (1792-1871), the English mathematician and scientific mechanician, had developed such an instrument in 1847; but it was announced with only brief comment — that its use had not increased efficacy of treatment. Babbage did not pursue his idea.

Sir William Osler and the Medical Library. Part I and II. Bull. Med. Libr. Assoc. 49:24-41, Jan.; 127-148, Apr., 1961.

This is the story of Sir William Osler, his interest, work, and efforts in behalf of the medical library profession. Librarian Keys divides Osler's career into four periods: (1) the Canadian period (Toronto and Montreal, 1869-1884), (2) the Philadelphia period (1885-1889), (3) the Baltimore period (1889-1905), and (4) the Oxford period (1905-1919). Throughout this chronology is woven Osler's interest in and contributions to libraries and librarians of each community in which he lived. Recounted are Osler's involvements with the Association of Medical Librarians and its successor, the Medical Library Association. This includes a very good history of the origin and infancy of the Medical Library Association. It is easy to see why Osler is so revered by medical librarians — he had much empathy for his "philobiblon" colleagues and their labors.

Edward Revere Osler, 1895-1917. Arch. Intern. Med. 114:284-293. Aug., 1964.

Plot 4, Row F in a Flanders field near Poperinghe provides the final resting place for the beloved son of the Oslers. This is a poignant account of Sir William's love for and close relationship with his son, Revere, killed on a battlefield in Flanders. Osler wrote the following note, which appears in Tom Keys's article, p. 292:

> A sweeter laddie never lived, with a gentle loving nature. He had developed a rare taste in literature and was devoted to all my old friends in the spirit — Plutarch, Montaigne, Browne, Fuller, and above all Izaak Walton, whose *Compleat Angler* he knew by heart and whose "Lives" he loved. We are heart broken, but thankful to have the precious memory of his loving life.

The College of the Medical Book: George Dock Lecture on the History of Medicine, Sponsored by the Los Angeles County Medical Association, Los Angeles, California, March 31, 1966. Part 1 and 2. Bull. Los Angeles County Med. Assn. 96:16, 24-25, 31, Dec. 1; 23, 26-28, Dec. 15, 1966.

The concept "The College of the Medical Book" uniquely epitomizes a lifetime of study, thought, and writing directed to the problem of how one should master a learned discipline like medical librarianship. This paper should provoke introspective thought on the part of a truly devoted philobiblon.

The Printed Word in Biomedical Communication. Ann. N.Y. Acad. Sci. 142:415-420, Mar. 31, 1967.

Dr. Keys presents his impressions on the strength and limitations of the printed Word in biomedical communication. Especially interesting are the comments on the barriers to good communication.

Sir Humphry Davy and His Safety Lamp for Coal Miners. Mayo Clin. Proc. 43:865-891, Dec., 1968.

Here is a delightful article about one of the author's heroes. Davy contributed much to the world of medicine with his observations and inventions. The safety lamp for coal miners was important to the rapid growth of the coal industry. Keys outlines the controversies of authorship regarding the invention of the safety lamp and supports Davy's claims. Davy's experiments and book pertaining to nitrous oxide, published in 1800 when Davy was 21, clearly portray genius. In that work he suggests that the gas be used for surgical anesthesia, an idea not adopted until much later.

Dr. Henry Stanley Plummer (1874-1936) (Historical Vignette). Minn. Med. 55:957-965, Oct., 1972.

This is an interesting personal account of one of the Mayo Clinic greats. The vignette recounts the qualities of a man about whom "Dr. Will Mayo himself said the hiring of Henry Plummer was the best day's work he ever did for the Clinic."[2]

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1. McDaniel WB II: Thomas E Keys, President, Medical Library Association, 1957-1958. Bull Med Libr Assoc 45 575, 1957

2. Clapesattle H. The Doctors Mayo. Second edition. Minneapolis, University of Minnesota Press, p 215, 1954

Second Annual Competition for Bush Clinical Fellowship
Application due date: March 1, 1980

Up to fifteen *primary care* physicians from *non-Metropolitan* areas of Minnesota will be selected to receive grants. The purpose of these grants is to enable physicians to take 6- to 12-month, "sabbatical"-type leaves from their practices in order to improve clinical, administrative and leadership skills that would enhance health care delivery in their respective communities and also further their own professional goals. For more information and application forms, please write to The Bush Clinical Fellows Program, Box 715, 420 Delaware Street SE, Minneapolis, Minnesota 55455 (phone 612/373-8012).

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due to susceptible strains of staphylococci and/or streptococci...

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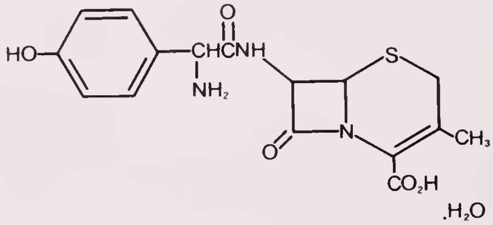
References:
1. Data on file, Mead Johnson Pharmaceutical Division.
2. Gatley MS To be taken as directed. *J Roy Coll Gen Pract* 16 39. 1968.

DESCRIPTION: DURICEF® (cefadroxil monohydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 7-[[D-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid monohydrate. It has the following structural formula:



Clinical Pharmacology–DURICEF (cefadroxil monohydrate) is rapidly absorbed after oral administration. Following single doses of 500 and 1000 mg., average peak serum concentrations were approximately 16 and 28 mcg./ml., respectively. Measurable levels were present 12 hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1800 mcg./ml. during the period following a single 500 mg. oral dose. Increases in dosage generally produce a proportionate increase in DURICEF urinary concentration. The urine antibiotic concentration, following a 1 gm. dose, was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.

MICROBIOLOGY: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. DURICEF is active against the following organisms *in vitro*:

- *Beta-hemolytic streptococci*
- *Staphylococci*, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
- *Streptococcus (Diplococcus) pneumoniae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Klebsiella* species

Note–Most strains of *Enterococci (Streptococcus faecalis* and *S. faecium)* are resistant to DURICEF. It is not active against most strains of *enterobacter species*, *P. morganii*, and *P. vulgaris*. It has no activity against *Pseudomonas* or *Herella species*.

Disc Susceptibility Tests–Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One recommended procedure (CFR Section 460.1) uses cephalosporin class disc for testing susceptibility; interpretations correlate zone diameters of the disc test with MIC values for DURICEF. With this procedure, a report from the laboratory of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if the infection is confined to the urinary tract, as DURICEF produces high antibiotic levels in the urine.

INDICATIONS: DURICEF (cefadroxil monohydrate) is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

- Urinary tract infections caused by *E. coli*, *P. mirabilis*, and *Klebsiella* species
- Skin and skin structure infections caused by staphylococci and/or streptococci

Note–Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATION: DURICEF (cefadroxil monohydrate) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNING: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE.)

Any patient who has demonstrated a history of some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exception should be made with regard to DURICEF (cefadroxil monohydrate).

PRECAUTIONS: Patients should be followed carefully so that any side-effe or unusual manifestations of drug idiosyncrasy may be detected. If a hypers sitivity reaction occurs, the drug should be discontinued and the patient treat with the usual agents (e.g., epinephrine or other pressor amines, antihistamin or corticosteroids).

DURICEF (cefadroxil monohydrate) should be used with caution in the preser of markedly impaired renal function (creatinine clearance rate of less than ml/min/1.73M²). (See Dosage and Administration.) In patients with known suspected renal impairment, careful clinical observation and appropriate la oratory studies should be made prior to and during therapy.

Prolonged use of DURICEF may result in the overgrowth of nonsusceptil organisms. Careful observation of the patient is essential. If superinfection occ during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with t cephalosporin antibiotics. In hematologic studies or in transfusion cross-mat ing procedures when antiglobulin tests are performed on the minor side or Coombs testing of newborns whose mothers have received cephalosporin ar biotics before parturition, it should be recognized that a positive Coombs t may be due to the drug.

USAGE IN PREGNANCY: Although no teratogenic or anti-fertility effects w seen in reproductive studies in mice and rats receiving dosages greater than t normal human dose, the safety of this drug for use in human pregnancy has been established. The benefits of the drug in pregnant women should be weigh against a possible risk to the fetus.

ADVERSE REACTIONS: Gastrointestinal–The most frequent side-effect has be nausea. It was infrequently severe enough to warrant cessation of therapy. Adm istration with food decreases nausea and does not decrease absorption. Diarrh and dysuria have also occurred.

Hypersensitivity–Allergies (in the form of rash, urticaria, and angioedema) ha been observed. These reactions usually subsided upon discontinuation of t drug.
Other reactions have included genital pruritus, genital moniliasis, vaginitis, a moderate transient neutropenia.

DOSAGE AND ADMINISTRATION: DURICEF (cefadroxil monohydrate) is a stable and may be administered orally without regard to meals. Administrati with food may be helpful in diminishing potential gastrointestinal complai occasionally associated with oral cephalosporin therapy.

Adults–For urinary tract infections the usual adult dosage is one gm. (two 5 mg. capsules) two times per day. For skin and skin structure infections the us dose is 500 mg. two times per day or 1 gm. once a day.

In patients with renal impairment, the dosage of cefadroxil should be adjust according to creatinine clearance rates to prevent drug accumulation. The f lowing schedule is suggested. In adults, the initial dose is 1 gm. of DURIC (cefadroxil monohydrate) and the maintenance dose (based on the creatini clearance rate [ml/min/1.73M²]) is 500 mg. at the time intervals listed bel

Creatinine Clearances	Dosage Interval
0-10 ml/min	36 hours
10-25 ml/min	24 hours
25-50 ml/min	12 hours

Patients with creatinine clearance rates over 50 ml/min may be treated as if th were patients having normal renal function.

Children–Dosage and safety have not yet been established in children.

HOW SUPPLIED: DURICEF® (cefadroxil monohydrate) capsules 500 mg. oral administration in an opaque maroon cap and opaque white body No. 0 ha gelatin capsule. On each half capsule printed in black is "MJ" and "500." Availat in bottles of 24 capsules (NDC 0087-0784-41) and 100 capsules (NDC 008 0784-42).

U.S. Patent Re. 29,164

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Medicine Grand Rounds

Laparoscopy in Internal Medicine

LAWRENCE R. KAPLAN, M.D.*
EDITOR: ROBERT J. McCOLLISTER, M.D.†

Dr. Dodd Wilson:

This morning at Grand Rounds I am pleased to introduce a new member of the faculty, Dr. Lawrence Kaplan, who has recently joined the Department of Medicine in the section of gastroenterology. Dr. Kaplan plans to be active in teaching and developing of new areas of clinical service and research. This morning he will discuss laparoscopy, a procedure not recently used in internal medicine in the United States. This technique has an obvious potential to assist physicians in patient care.

Dr. Lawrence Kaplan:

In the past decade ingenious techniques and new instruments have improved the accuracy of diagnosis of abdominal disease. Procedures such as endoscopic retrograde cholangiopancreatography (ERCP), computerized tomography scanning (CT), and ultrasonography (ECHO) are now commonly employed. Yet, even as we order these tests we all recognize that no procedure is innocuous and all involve certain costs and risks which must be assessed in relation to the benefit to the patient. ERCP has a low but definite morbidity and mortality and a CT scan, although non-invasive, is expensive. We must then carefully consider each technique, especially those newly introduced, in light of both medical ethics and medical economics. In so doing, these three questions must be answered: (1) Does the procedure yield predictable, reliable findings? (2) Does the procedure have distinct advantage over simpler, less costly or less invasive methods already in use? (3) Does the procedure favorably alter patient care? In this presentation on laparoscopy, I shall discuss each of these three important questions.

In laparoscopy, the peritoneal cavity and its contents can be viewed through an endoscope which has been passed through the anterior abdominal wall after the introduction of a pneumoperitoneum. Since the laparoscope can be used for directed biopsy, this procedure can provide not only visual but also histologic information concerning intraperitoneal disease.[1,2]

Laparoscopy#, which is synonymous with peritoneoscopy, was first described in 1902 by Kelling, a Dresden surgeon who used it in experiments on dogs. Eight years later, both Kelling and Jacobeas, a Swedish surgeon, reported using the method in humans. Laparoscopy has been widely used in clinical gastroenterology in Europe for over 50 years. However, except for gynecologists, the procedure is remarkably underutilized by physicians in the United States.

Gastroenterologists usually perform laparoscopy in an endoscopy room rather than in a surgical suite. First, the procedure is discussed with the patient and informed consent obtained. Then, routine laboratory studies including complete blood count with estimation of platelets, a prothrombin time, and an electrocardiogram are obtained. No bowel preparation is necessary. The patient is given atropine (0.6 mg IV) and diazepam (2-5 mg IV) immediately prior to the procedure.

Laparoscopic technique has changed little since its introduction 75 years ago. The patient is placed in a comfortable, supine position and the abdomen is prepped with antiseptic and covered with a sterile drape. Local anesthesia is obtained using 2% xylocaine which is injected into the skin and subcutaneous tissue at a selected area around the umbilicus. A special pneumoperitoneal needle designed to avoid bowel perforation is then pushed through the abdominal wall. A pneumoperitoneum is established with nitrous oxide, a gas which is rapidly absorbed across the peritoneum. Carbon dioxide is occasionally used but is less desirable in the conscious patient because it causes diaphragmatic pain. The rate of gas flow, the total volume of gas given, and the intraabdominal pressure are monitored and regulated during the procedure. The average patient requires 2½ to 4 liters of gas for an adequate pneumoperitoneum. Once the pneumoperitoneum has been created, a sheathed trocar (Figure 1, upper) is advanced through the abdominal wall. The sheath of the trocar has an automatic value to prevent

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#To the purist the term laparoscopy is a misnomer, an abomination rather than an abdominal examination. The Greek root "lapara" refers to the soft part of the body between the ribs and the hips, i.e. the flanks. Therefore, peritoneoscopy, the examination of the peritoneal cavity, is the preferred term.

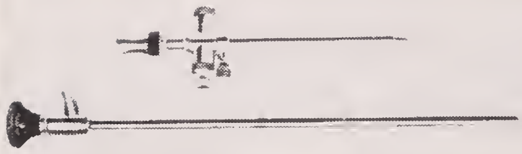

Figure 1

the loss of gas during insertion and removal of the laparoscope. The laparoscope (Figure 1, lower), can then be inserted through the sheath into the peritoneal cavity to view its contents (Figure 2).

What can be seen through the laparoscope? Approximately 70% of the liver surface is visible. One can also examine the lesser curvature and anterior wall of the stomach, the fundus of the gallbladder, portions of the small bowel, the inferior pole of the spleen, the cecum, the appendix if it is anterior, the inguinal canal and its contents, the pelvic organs, and most of the anterior and lateral peritoneal surface. Figure 3 shows the normal liver (left), adjacent lesser curve of stomach (right lower), diaphragm (above) with spleen tip (right). Diagnostic biopsies of the areas including the spleen can be obtained. Bleeding is controlled with direct pressure or electrocoagulation.

It is important to recognize that laparoscopy does not allow direct examination of retroperitoneal lymph nodes, the porta hepatis, the pancreas or the ureters. However, an enlarged retroperitoneal organ or mass can often be identified and biopsied.[3]

To end the examination, the gas is released, the sheath is removed, and the puncture site is closed with skin sutures or steristrip. The routine for postoperative care usually depends on whether or not biopsies are obtained. If biopsies are taken, the patient is admitted to the hospital for overnight observation. If not, the patient is observed for 2 to 3 hours and then is discharged. Laparoscopy with needle biopsy can be completed in approximately 30 minutes by an experienced operator. The patient should experience only minimal discomfort during the procedure and should not require postoperative analgesics.

The morbidity of laparoscopy is remarkably low. In one review of over 4000 cases, the morbidity was reported as 1% (Table 1). In those few patients in whom a complication occurs, it is most commonly either bleeding or subcutaneous emphysema.[4]

There are only a few patients in whom laparoscopy is absolutely contraindicated. These include individuals with mechanical or paralytic ileus, because of the increased risk of perforating a distended bowel, those with coagulation defects which cannot be corrected, acute myocardial infarction, and patients who are

TABLE 1

Complications of Laparoscopy (4459 cases)*

			%
Emphysema:	omental (7)		0.22
	subcutaneous (3)		
Perforation:	colon (2)		0.13
	small bowel (1)		
	gallbladder (1)		
	liver (2)		
Bleeding:	intraperitoneal (15)		0.65
	extraperitoneal (13)		
Infection			0.04
Metastatic implant			0.06
	Total	(49)	1.10%
Technically impossible		(61)	1.36
Mortality		(4)	0.08

*Van Waes, L (1973)[4]

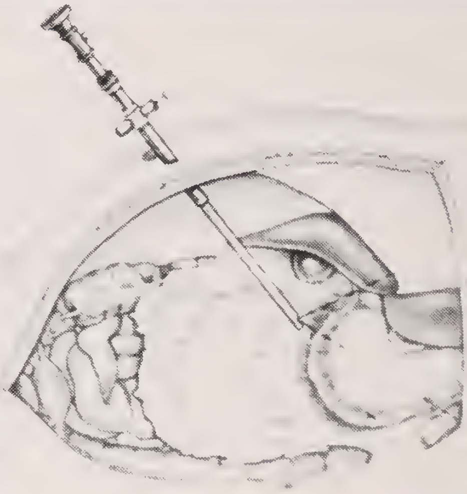

Figure 2

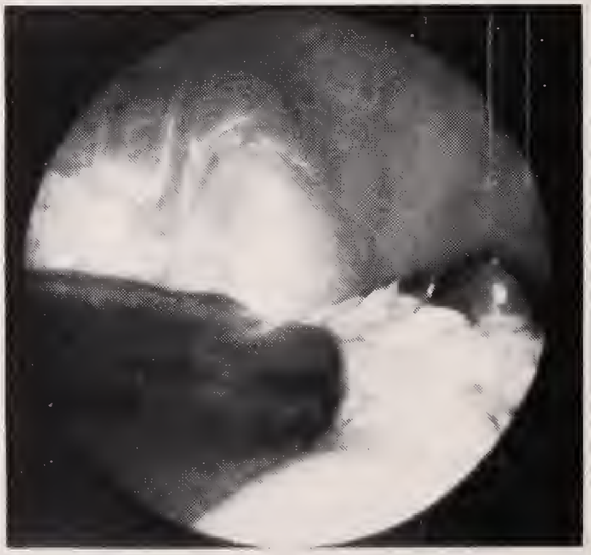

Figure 3

uncooperative. Relative contraindications include cardiovascular or respiratory insufficiency and abdominal wall infection. Prior abdominal surgery or ascites rarely present problems to the experienced laparoscopist.

What are the indications for laparoscopy in internal medicine (Table 2)? In gastroenterology, laparoscopy is used chiefly to diagnose hepatobiliary disease. In one study of 300 consecutive laparoscopies in patients with "liver disease," Portuguese investigators correctly diagnosed 95% of the problems.[5] Similar results are reported in other studies and support the conclusion that laparoscopy is an extremely useful diagnostic procedure. Figure 4 shows an enlarged nodular liver with chronic active hepatitis.

TABLE 2

Indications for Laparoscopy

- **Hepatobiliary Problems**
  - **liver function test abnormalities**
  - **hepatosplenomegaly**
  - **liver scan abnormalities**
  - **ascites**
  - **gallbladder abnormalities**
  - **extrahepatic obstruction**
- **Abdominal Problems**
  - **abdominal mass**
  - **splenic disease**
  - **peritoneal disease**
  - **abdominal pain: acute and chronic**
- **Malignancies and Metastases**
  - **staging**
  - **limits of operability**
- **Therapeutic**
  - **recovery of intraabdominal foreign body**
  - **lysis of adhesions**
- **Experimental**
  - **objective evaluation of response to therapy**

The point at which laparoscopy should be used in patients with a hepatobiliary problem is controversial. In Europe, laparoscopy is often the first choice among the specialized, technical procedures. I do not agree with this approach. Certainly other less invasive, less costly procedures as ERCP, abdominal CT scan, or percutaneous liver biopsy may obviate the need for laparoscopy in some patients. However, a certain percentage of patients will require histologic confirmation of disease and a laparoscopy with directed biopsy can provide that information. I believe we shall be able to identify a group of patients with a constellation of physical findings and laboratory abnormalities who, if subjected to laparoscopy, can be diagnosed promptly and thereby eliminate a lengthy and costly workup.

Other diagnostic indications for laparoscopy include the evaluation of abdominal masses, splenic abnormalities, peritoneal disease with ascites, and chronic pain. In some medical centers a miniature laparoscope is used in the emergency room to diagnose acute abdominal pain.[6] In this way, a number of patients with pelvic inflammatory disease mimicking acute appendicitis have been spared surgery.

Laparoscopy is an alternative to exploratory surgery in selected cases. In 145 patients scheduled for surgery following extensive diagnostic workup for abdominal disease, Trujillo[7] established a diagnosis in over 90% with laparoscopy, thereby obviating the need for surgery.

Laparoscopy is also used to stage malignancies such as carcinoma of the esophagus, breast or lung and to evaluate the limits of operability.[8] In a study of Hodgkin's disease with liver involvement, laparoscopy with directed biopsy was as effective as laparotomy with wedge biopsy in the staging of liver disease.[9] Laparoscopy has the added advantage over laparotomy in that chemotherapy or radiotherapy can be started immediately, often on an outpatient basis, once a diagnosis is made.

The therapeutic indications for laparoscopy include the recovery of foreign bodies and lysis of adhesions. Laparoscopy can be performed repeatedly in the same patient without danger of producing adhesions.

What about those three questions which must be addressed to evaluate any new diagnostic technique? (1) Does laparoscopy yield predictable, reliable findings? Yes, with a diagnostic yield over 90%. (2) Does laparoscopy have distinct advantages over simpler, less costly or less invasive methods already in existence? Yes, particularly when a tissue diagnosis is

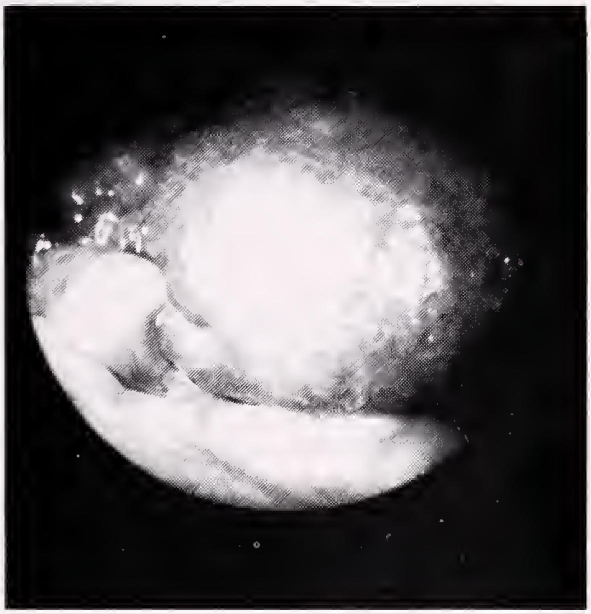

Figure 4

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required. (3) Does laparoscopy favorably alter patient care? Yes, in cases when exploratory surgery is avoided, when treatment can proceed without delay or when the accuracy of a tissue diagnosis is crucial to development of the best possible therapeutic plan.

Question: What will diagnostic laparoscopy cost?
Answer: I estimate the cost at $350-400. This includes the professional fee and charge for use of the treatment room.

Question: How does the morbidity of a closed percutaneous biopsy compare with a directed biopsy during laparoscopy?
Answer: The morbidity is approximately the same, particularly when the closed biopsy is preceded by a liver-spleen scan. Some endoscopists, however, claim that the incidence of post biopsy hemorrhage is less after a laparoscopy because you can control bleeding with direct pressure or electrocoagulation.

Question: What is the role of closed percutaneous biopsies in diagnosing liver disease?
Answer: The problem of sampling error is always a concern, but when the liver is diffusely involved with disease as in the case of hepatitis, hemochromatosis, or cirrhosis, a "blind" biopsy will probably give the diagnosis. However, when you suspect limited focal involvement of the liver, a closed percutaneous biopsy is a low-yield procedure.

Question: Is laparoscopy a substitute for ERCP or "skinny needle" in evaluating patients with jaundice?
Answer: No. I do not feel comfortable differentiating extrahepatic versus intrahepatic jaundice on the basis of the gross appearance of the liver. If extrahepatic obstruction is suspected, the biliary system should be directly examined with either ERCP or percutaneous cholangiography. When extrahepatic obstruction is diagnosed, knowledge of the ductal architecture is a valuable aid to the surgeon.

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MINNESOTA MEDICINE

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(Continued to page 906)

Fracture Conference

Treatment of Ununited Fractures Adjacent to Joints

FRANK C. HUI, M.D.*; MARK B. COVENTRY, M.D.†; GEORGE D. VEASY, M.D.*
and
MIGUEL E. CABANELA, M.D.†

Dr. Mark B. Coventry:

In ununited fractures adjacent to joints, the first goal is to obtain union, the second is to obtain union in almost anatomic position, and the third is to keep function in the adjacent joint. To accomplish these, fixation is usually needed. The following cases illustrate these points at the shoulder, hip, knee, and ankle.

Case 1

Dr. Frank C. Hui:

A 55-year-old woman injured her right shoulder in August 1966 during a fall. She was treated at another institution by open reduction and internal fixation. She was seen at the Mayo Clinic about one year after the injury because of severe shoulder pain, and this was the roentgenogram taken at that time (Figure 1A).

Dr. Coventry: Dr. Hathaway, what would you suggest to obtain internal fixation?

Dr. Frederick D. Hathaway: The rod and band should be removed and probably a small plate with *bone grafts* should be used.

Dr. Coventry: The proximal fragment seems large enough for that.

Dr. Hui:

The pseudarthrosis was resected, and the fragments were secured by *double bayonet apposition* and were plated. An autogenous iliac bone graft also was applied. A shoulder spica cast was worn by the patient postoperatively for about two months, and union occurred (Figure 1B).

Dr. Coventry:

I did not have enough confidence in internal fixation to use it without the spica cast, and the combination was successful. If the plate had been used alone with the very small proximal fragment, it might have loosened.

Case 2

Dr. Hui:

A 64-year-old woman fell from a horse in June 1966, sustaining a closed fracture of the neck of her left humerus. Initially, she was treated by closed reduction at another institution, and two weeks after the injury, an open reduction was performed there. No internal fixation was used. Immobilization for about two months was achieved by a Velpeau dressing, after which range of motion and muscle building exercises were instituted. However, the patient continued to have severe pain in her shoulder and progressively decreasing range of motion. She decided on further consultation about 10 months after the injury, and these were the initial roentgenograms (Figure 2A and B).

Dr. Coventry:

At the initial treatment, it was reported that the distal fragment was able to be pushed into the head; and it held securely, so internal fixation was not used. Yet, the distraction forces separated the fragments. Dr. Gross, is the humeral head viable? Can you tell by these roentgenograms?

Dr. Richard M. Gross: The head of the humerus appears to be viable.

Dr. Coventry:

I wonder what was nourishing the head. I suppose there were enough soft-tissue adhesions to supply

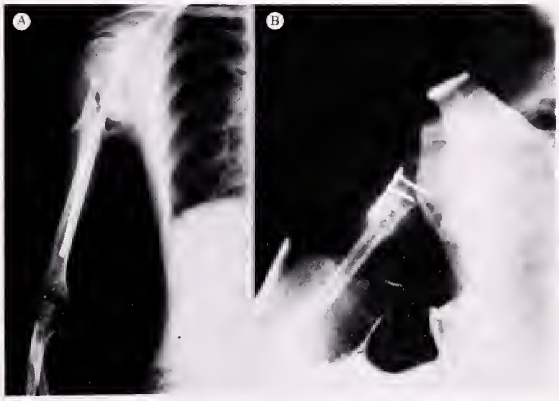

Fig. 1 (Case 1). A 55-year-old woman with nonunion of proximal humeral fracture. (A) One year after primary open reduction and internal fixation done at another institution. (B) Two months after double bayonet apposition, plating, and iliac bone grafting. Bony union is present.

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Fracture Conference, November 10, 1976

some blood. At this time, it was 10 months after the injury, and one might expect a vascular necrosis to have occurred, if it was going to.

Dr. Gross:

In a situation like this, one can probably replace the head fragment with a Neer prosthesis. One can osteotomize the tuberosities with the muscles attached and then put the prosthesis in and gather the tuberosities around the prosthesis.

Dr. Coventry: What happens if muscles of the cuff are not present?

Dr. Gross: The prosthesis dislocates.

Dr. Coventry:

That's true, and it dislocates anteriorly because of the pull of the pectoralis major muscle. So one must have an adequate cuff to expect a Neer prosthetic replacement to be successful. What would you do in this case, Dr. Cofield?

Dr. Robert H. Cofield:

Most patients with these injuries have rotator cuffs. You have a fracture of the greater tuberosity here, which indicates that the failure occurs through bone rather than muscle.

Dr. Coventry: If we were confronted with this problem before a Neer prosthesis was used, what should we have done?

Dr. Cofield: How old is the nonunion?

Dr. Coventry: Ten months.

Dr. Cofield:

One could do what was done in the previous case. If the anatomy was favorable when the fracture was exposed, the head could be held in place with pins or tension wires. I think it might be worth trying.

Dr. Coventry:

Perhaps some intramedullary Rush pins and then a figure-of-eight tension wire could be used. Is that your intent?

Dr. Cofield:

Yes, a figure-of-eight wire about pins should be placed through the head proximally and the shaft distally.

Dr. Coventry:

We have done this in another case, and it has worked successfully. An alternative procedure is to make some type of internal fixation device that can be inserted into this small head and that can secure the head to the distal fragment. And that was what we used.

Dr. Hui:

The pseudarthrosis was resected, and the fragments were secured by a blade plate. The fixation was enhanced by three iliac bone grafts, which were placed along the shaft and into the head. Cancellous bone chips also were applied, and a shoulder spica cast was worn for about 4 months. Bony union was achieved (Figure 2C).

Dr. Coventry:

In this case, I was also conservative and applied a spica cast, although it may not have been needed. A two-year follow-up revealed that the patient was back at skiing and leading a vigorous life. This case emphasizes, in part, that one need not necessarily take out the head of the humerus and put in a prosthesis. The patient had a good shoulder joint, which is important. If she had a poor joint or avascular necrosis, a prosthesis would have been indicated. Interestingly, no one suggested that the head be removed and the joint left flail. Such patients do very poorly from the standpoint of pain relief and function.

Case 3

Dr. Hui:

A 61-year-old man had an intertrochanteric osteotomy done in 1968 for degenerative arthritis of the right hip. A plate was initially used for fixation. The plate broke about seven months after the operation, and the patient had another operation in which a nail plate was used for fixation. He continued to have severe pain in the right hip and came to the Mayo Clinic for consultation. This roentgenogram was taken at that time (Figure 3A).

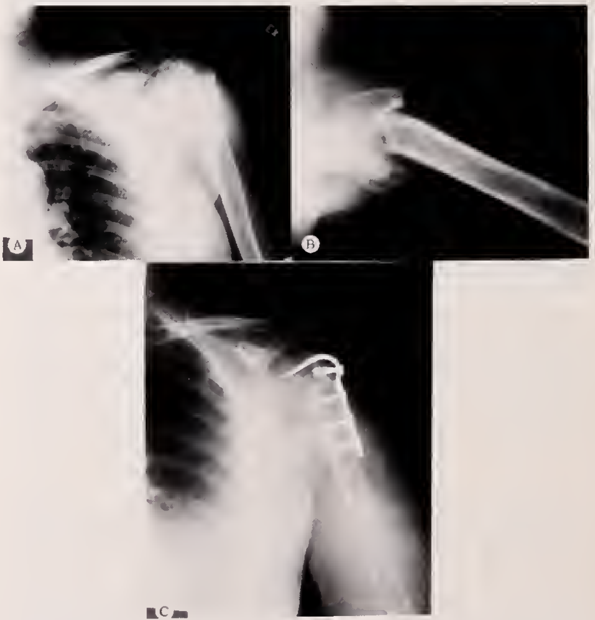

Fig. 2 (Case 2). A 64-year-old woman with nonunion of proximal humeral fracture. (A) Anteroposterior view. (B) Axillary view. (C) Four weeks after fixation with blade plate and bone graft. Bony union is present.

Dr. Coventry: There is an established intertrochanteric nonunion located just below the neck.

Dr. Patrick W. Bowman: The joint itself is bad, in addition to the established nonunion. This probably could be reconstructed with total hip arthroplasty.

Dr. Coventry:

I think your point about the joint being involved is pertinent. Fortunately, hip replacement should solve both problems, the nonunion and the arthritic hip (Figure 3B). At the time of this fracture, we had no custom prostheses and no long-neck prostheses, so we built up the length with methacrylate. Today this would not be done, but nonetheless the prosthesis has held up for five years, with no sign of weakening from failure of the cement and no sign of loosening.

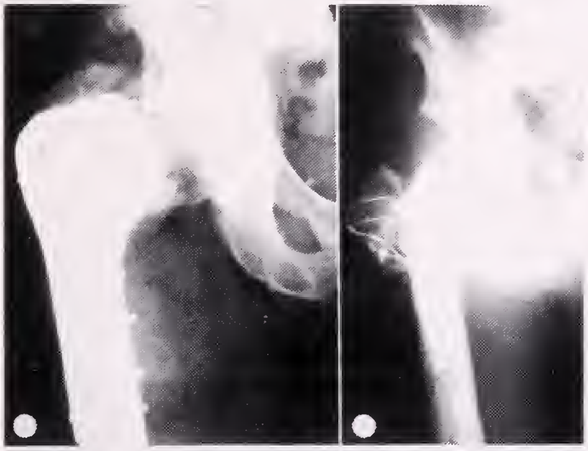

Fig. 3 (Case 3). A 61-year-old man with nonunion of proximal femur. (A) After intertrochanteric osteotomy done in another institution for degenerative arthritis of right hip. (B) After total hip arthroplasty. Greater trochanter has united to femur.

Case 4

Dr. Hui:

An 86-year-old woman sustained a fracture of the right hip during a fall in July 1975. She was initially treated at another institution with open reduction and internal fixation. However, she continued to have significant pain in her right hip. She came to the Mayo Clinic for further treatment. She was found to have a nonunion at the fracture site as well as severe degenerative arthritis of the hip joint (Figure 4A). Total hip arthroplasty was done, and she had good relief of pain and was doing very well after the operation (Figure 4B).

Dr. Coventry:

Here is a little different problem. We did not need to remove the trochanter for exposure. When we can leave on the trochanter, we should; then we do not have the problem of putting the trochanter back on cement or even to metal or both. We could get good exposure with external rotation and downward traction. The CAD prosthesis added strength that was needed at stress vulnerable areas. I am concerned about the bony support, but there probably is enough femoral fixation so that should not be a problem. Because the patient is 86-years-old, she is not going to stress this very much. But if she were 56 years old and weighed 200 lb, I would be worried about a long-term result.

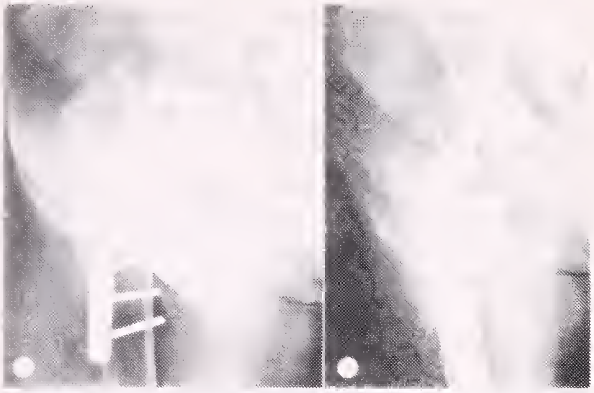

Fig. 4 (Case 4). An 86-year-old woman with nonunion of right proximal femur. (A) After open reduction and internal fixation of proximal femoral fracture done at another institution. (B) After total hip arthroplasty.

Case 5

Dr. Hui:

A 70-year-old woman sustained a proximal femoral fracture from a fall about 2 years prior to being seen at the Mayo Clinic. She was treated by use of a nail plate.

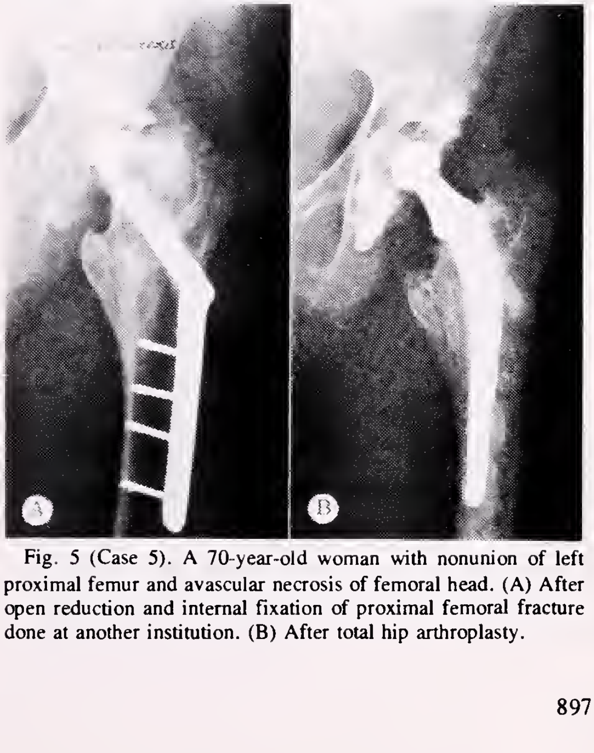

Fig. 5 (Case 5). A 70-year-old woman with nonunion of left proximal femur and avascular necrosis of femoral head. (A) After open reduction and internal fixation of proximal femoral fracture done at another institution. (B) After total hip arthroplasty.

She continued to have severe pain in the left hip after the operation. She was found to have a nonunion of the fracture, together with avascular necrosis of the femoral head (Figure 5A). Total hip arthroplasty was performed (Figure 5B).

Dr. Coventry: When we saw her, the intertrochanteric fracture had healed and there was an ununited neck fracture and avascular necrosis of the femoral head. The reconstruction was straightforward.

Case 6

Dr. Hui:

A 56-year-old physical education instructor was involved in a pedestrian-automobile accident one year prior to being seen at the Mayo Clinic. She sustained a dislocation of the left hip and a compound fracture of the left proximal tibia. The left hip was treated by closed reduction, and the left tibial fracture was treated initially by debridement, open reduction, and delayed primary closure. When first seen, she had a few draining sinuses, a clinically movable fracture, and a footdrop (Figures 6A and B).

Dr. Coventry:

This patient was badly injured and had a compound fracture. The referring physician said that he despaired of saving this limb at the time because of the hemorrhage, which could not be controlled. He found the anterior tibial artery was bleeding vigorously halfway down the leg. So he packed it to control the bleeding, and then he did a delayed primary closure.

Dr. Stephen G. Taylor: The patient has an ununited upper tibial fracture. I am concerned about the joint which appears to be bad.

Dr. Coventry: There was drainage. The fracture appeared to be a compound one. Cultures showed *Staphylococcus aureus*.

Dr. Taylor: Then the first thing to do would be to debride this area once more to try to get it cleaned up.

Dr. Coventry:

A couple of things concern me. If this was a compound fracture and we have to effect a union, we do not want infection at the site of the internal fixation. So the first priority is to clear up the infection. We were also concerned about the presence of a foreign body. We explored the fracture. I expected the sinus to go into the fracture site. And much to my amazement, the sinus communicated with the anterior tibial compartment and not the fracture. There was an abdominal pack present, and the roentgenographic shadow was the radiopaque marker of the pack. So, we did not have a compound fracture. We had an infected leg, but the fracture site itself was not contaminated. We took out the pack and curetted the anterior crural compartment of granulation tissue. We packed the compartment, and then did a delayed closure. The wound healed promptly. The patient went home for the usual conservative program. How long after that did we get back to the fracture?

Dr. Hui: Five months.

Dr. Coventry: How should the nonunion be treated?

Dr. Taylor: The location makes it somewhat difficult to get a secure hold of the proximal fragment.

Dr. Coventry: Obliquity may help you. How would that help?

Dr. Taylor: You could put bicortical screws in or use a blade plate.

Dr. Coventry: Or both. You do not have to worry much about the anterior tibial artery because that is gone.

Dr. Hui: A blade plate was used, and a bone graft was applied (Figures 6C and D).

Dr. Coventry:

The fibula was in the way, and there was some shortening. We wanted to remove the fibular head and

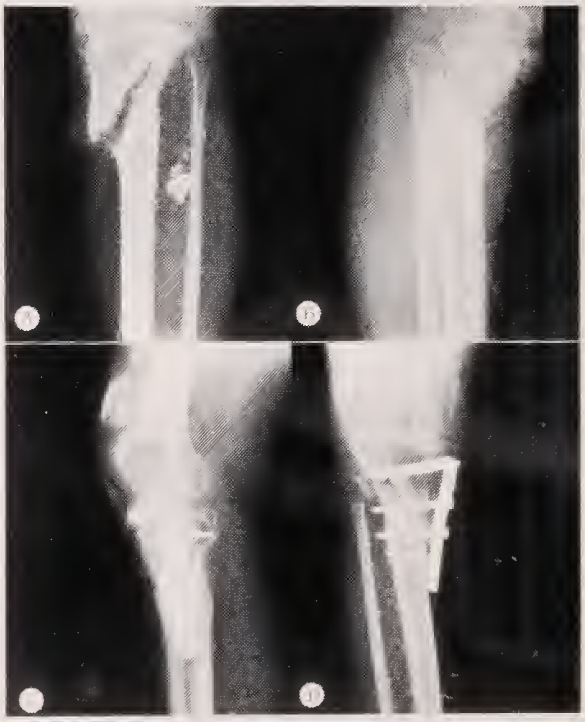

Fig. 6 (Case 6). A 56-year-old woman with compound fracture of left proximal tibia. Roentgenogram taken 1 year after debridement, open reduction, and delayed primary closure done at another institution. Nonunion is still present. Foreign body is seen in anterior compartment. (A) Anteroposterior view. (B) Lateral view. (C) and (D) Fixation with blade plate 5 months after debridement resulted in bony union. (C) Lateral view. (D) Anteroposterior view.

explore the peroneal nerve because we were still not sure whether the footdrop was due to the anterior compartment syndrome or whether it was due partly to the anterior compartment syndrome and partly to peroneal nerve palsy. We explored the peroneal nerve, and it was normal. The fibular head was used as a graft. The patient did obtain a union. She has no pain in her knee and can walk. Recently, we transferred the posterior tibial tendon anteriorly as a dorsiflexor to correct her footdrop.

Dr. Franklin H. Sim: Did you consider using knee arthrodesis as part of the primary reconstruction?

Dr. Coventry:

No. We preferred to maintain motion in the knee. Actually, her knee is practically symptomless now. She walks as much as she wishes. But I think she will have more trouble as she ages. Then we can consider arthroplasty.

Case 7

Dr. Hui:

A 40-year-old very athletic patient was injured in a skiing accident and sustained a compound fracture of the left distal fibula and tibia. Initially, he was treated with pins in the tibia and calcaneus, and the leg was incorporated in a cast. Two weeks later, open reduction and internal fixation were performed (Figures 7A and B). A wound infection developed postoperatively with *S. aureus*. The infection was treated with intravenously administered oxacillin and suction-irrigation, and the infection eventually cleared. The patient's main complaint was that he had to walk on the outside of his foot; pain was not a significant feature. Examination revealed 25° of ankle varus and 20° of internal rotation of the tibia. Motion was only 5° of dorsiflexion and 5° of plantar flexion. The left lower extremity also was somewhat shorter than the right.

Dr. Coventry:

This patient was very active and athletic. He exercised two or three hours a day. He walked on the outside of his foot due to varus, and he has 20° of internal rotation of his tibia. That is a lot of internal rotation, and he certainly is "pigeon-toed." He was worried for he could not ski, he could not play paddleball, he could not play tennis, and he could not jog. He is young, and he may suffer serious foot problems if the ankle varus persists. I felt that he had a nonunion. Rather than going directly to ankle fusion, we took another course. We corrected all of the deformity by osteotomy, not only the varus but also the internal rotation. The distal fragment could only take two pins and the proximal, three pins. The Hoffman apparatus was then attached. A type of osteotomy that is generally effective in these situations was done. The procedure was half "open" wedge and half "closed" wedge, which gives a good bone-to-bone surface apposition and does not sacrifice much length (Figure 7 C). Union is not yet present, and it may be considerably delayed because of the sclerotic nature of the bone. I think this is an ideal situation for the Hoffman unit. I know of nothing else to use that would do as good a job as this — maintain compression and position and allow complete mobilization of the ankle joint.*

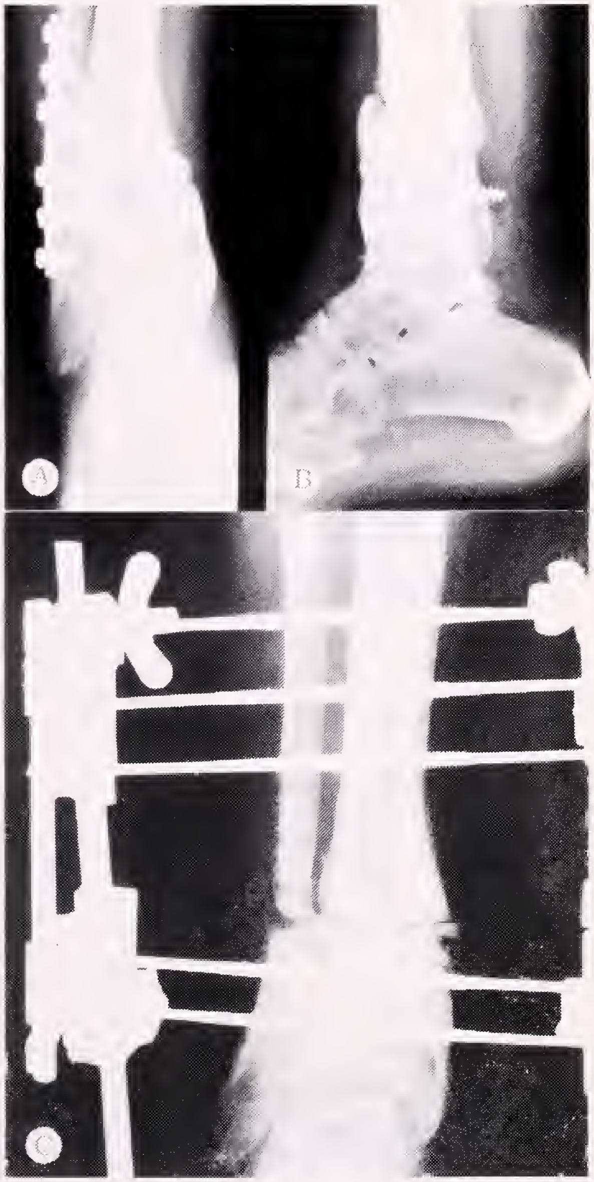

Fig. 7 (Case 7). A 40-year-old man with nonunion of distal tibia and fibula one year after open reduction and internal fixation of compound distal tibia and fibula fracture done at another institution. (A) Anteroposterior view. (B) Lateral view. (C) Osteotomy and fixation with Hoffman apparatus.

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*Since the writing, firm union of the osteotomy has occurred.

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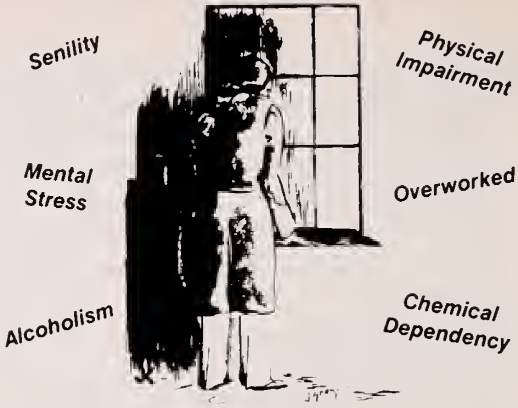

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Neurology

An Efficient Approach to the Mental Status Examination

BRUCE D. SNYDER, M.D.*

The neurologic mental status examination is outlined and the rationale for the various subtests discussed. The importance of the mental status examination for evaluating metabolic and degenerative disease of the nervous system is emphasized. Interpretation of findings of the mental status examination is discussed.

THE MENTAL STATUS examination (MSE) remains perhaps the most sensitive procedure available for the diagnosis of metabolic and degenerative disease of the cerebral hemispheres. In many instances, special studies (e.g. the CT scan) cannot be clinically interpreted without an accurate MSE. The early recognition of postoperative or post-traumatic confusion, prehepatic encephalopathy, CO_2 narcosis, etc. is materially aided by the ability to do a MSE. The distinction between functional overlay and actual organic disease can be more easily made when one is familiar with these techniques and their interpretations. Like any other part of the physical examination, MSE is used as a problem-solving tool, flexibly fashioned to answer the particular question posed by the individual patient. The physician requires a conceptual framework for using the MSE which will permit him to modify the examination for efficient use. Unfortunately, many physicians view the MSE as a series of odd maneuvers and questions which appear to take a great deal of time and don't seem to add up to any clinically useful statement about the patient. Students demonstrate the ability to answer specific questions about MSE tests but, when observed in practice, have no well-thought-out approach which permits them to reach a conclusion within a reasonable amount of time.

This paper is an attempt to clarify the rationale for using the MSE in screening for neurologic disease. The exam will be discussed in two parts: first, a general survey of such non-localizable functions as thought, affect, judgment and insight, and then a review of screening tests for focal cerebral disease. Interpretation will be briefly discussed after outlining each portion of the MSE. Finally, I will conclude with brief examples of typical patient responses, showing how the exam is modified to fit the need at hand.

It should be stressed that this outline, though hopefully accurate, reflects my personal bias and methods as well as an attempt to simplify the procedure for the non-neurologist.

The MSE is designed to answer several specific questions about the state of the patient: (a) Is cognitive (intellectual) and affective (emotional) functioning normal? (b) If not, is the impairment organic (due to identifiable disease of the nervous system), or is it psychogenic? (c) Is there evidence of focal (or multifocal) damage to the cerebral hemispheres? (d) Is the patient psychotic (in other words, unable to assess reality and the consequences of his actions or situation) and/or incompetent?

Conditions for testing should be optimized. Use a quiet, well lit area; if patients usually wear glasses, they should be put on. They all too often are in the bedside table along with the hearing aid. Hearing impaired patients may be able to use a stethoscope as an aid; the examiner speaks into the bell. Cerumen impactions may have to be removed. *Some knowledge of the patient's social and educational background is very important for accurate interpretation of findings.*

Conduct of the General Survey

The initial portion of the mental status exam requires relatively few specific questions but close observation and good listening. It especially requires that the patient's responses be compared to those expected of an *intact individual placed in the patient's situation.* The practitioner must generate his own admittedly subjective norms during his daily exposure to the many patients he sees.

The very first and possibly most important observation is an assessment of the level of consciousness. Labels such as "obtunded," "stuporous," or "lethargic" should be avoided as they are not clearly definable. A brief behavioral description such as "patient yawning and goes to sleep between questions," or "can only be aroused by pain and then

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merely fends off the examiner" is invaluable as it provides a clear baseline against which to measure future changes. If the patient is not alert, the interpretation of the rest of the mental status exam is altered. Memory, speech, and most other localizing tests decline in reliability. Additionally, the patient with an impaired level of consciousness must be considered a potential emergency requiring intensive monitoring.

The general appearance is noted: dishevelment, bizarre dress, evidence of incontinence are recorded. Affect is assessed: what sort of mood tone is present (e.g. euphoric, depressed), and is it *appropriate* to the patient's situation? This last point is crucial: all too often the patient who is tractable, quiet, and superficially pleasant is described as "appropriate" even though the patient's actual situation may warrant grief, anger, fear, or depression as a realistic response. Lability of affect should be noted: the patient who greets the physician effusively and then belligerently refuses examination is labile. Finally, thought processes are noted: what is the patient thinking about? Is he realistically concerned about his ailment? Is he having hallucinations or delusions? The former should be tactfully asked for; the latter may often be detected by reflecting back the patient's remarks and simply listening for a time. Do the patient's thoughts progress logically to deal with the question at hand, or does he "run out of gas?" Do thoughts wander tangentially or are conceptual relationships bizarre? Is the patient properly oriented?

Judgment and insight are often best assessed by looking at the patient's appreciation of his own situation and its problems. This is preferable to such stock questions as, "What would you do with a letter if you found it on the street?" Such contrived items are either too simple or fail to engage the patient's interest; in addition, many sample questions of this sort, like proverbs, are culture-specific. The patient should know or be concerned about where he will live (if he's hospitalized), how he can support himself, whether he can qualify for medical assistance, etc. Additionally, the use of realistic questions provides direct information about the patient's functional ability.

General Information — A few questions should be used to test the patient's fund of knowledge; these should be relevant to the patient's background. A patient of little means and education might be asked, for example, about bus fares or the cost of grocery items.

Interpretation of the General Survey

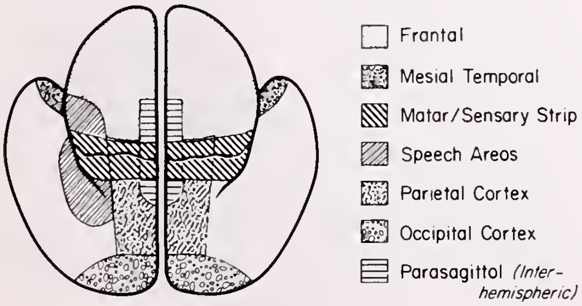
Thus far, we have gathered data about the patient's thought processes and affective state; this information can be analyzed to answer some of our initial questions and provide important guides to management and therapy. Organic brain disease may be due to a systemic metabolic disorder (e.g. uremia), a cerebral "degeneration" of unknown etiology (e.g. Alzheimer's disease), increased intracranial pressure, or multifocal destructive lesions (e.g. metastases, infarctions, etc.). The cardinal features of organic brain disease (dementia) are depression with or without paranoia, accompanied by initial lability of mood and progressing (at a rate reflecting the time course of the disease) to a flattening of the affect with ultimately little emotional expression whatsoever. During the phase of lability, mood swings tend to occur from minute to minute rather than over a course of weeks to months, as seen in primary affective disorders. Thought content is gradually reduced and progression of thought becomes abnormal, being initially tangential (a borderline abnormality which can be found in a number of "normal" individuals), but eventually failing to progress from concept to concept. Such a patient will demonstrate abrupt shifts from one concept to another and ultimately will not progress at all, i.e. will respond by word or phrase only, with virtually no ability to expand upon the thought at hand. There is loss or restriction of general knowledge that the patient should have. Hallucinations may be useful in characterizing the patient: primarily visual, highly realistic content points more towards organic disease whereas auditory, symbolic content is more suggestive of functional psychoses. Dishevelment may be seen in dementia, depression, or functional psychoses but is more likely to signify the former two groups. Incontinence is much more indicative of organic brain disease. Whether or not the patient is thought to be suffering from dementia, the detection of significant depression has definite implications for management. Additionally, judgment as to whether the patient is incompetent and/or psychotic will be important for planning and treatment. Performance may fluctuate over minutes to hours: very abrupt or rapid changes suggest epilepsy, transient ischemia, or psychogenic elements; fluctuations over hours to days are seen with metabolic encephalopathy or some mass lesions (e.g. subdural hematoma).

Among the most difficult clinical distinctions is that between advanced depression and dementia. The presence of dishevelment, lability, agitation, depressed mood, restricted thought content and progression, hallucinations and delusions, and impaired memory may be seen in either state. Disorientation, decline in fund of knowledge, and the presence of primitive reflexes, described in the "focal survey," may help signify organic disease. Ultimately, laboratory procedures and/or a clinical trial of ECT or antidepressants may be necessary. Parkinson's disease also enters the differential: masked facies may be taken for flat affect, and dysarthria may so limit expression that thought appears very limited. Additionally, advanced Parkinsonism is complicated by dementia. Again, results of general exam and therapeutic trial may be needed to clarify the situation.

Focal Survey — Rationale

For purposes of the bedside MSE, much of the cerebral hemispheres are clinically "silent;" certain regions are expressive, however, and yield symptoms and signs of focal dysfunction. Among the many "higher function" tests available, the clinician should choose a workable but comprehensive screening battery and organize this for efficient use. I will first present a survey of clinically assessable areas (Figure 1) followed by an outline of appropriate bedside examinations organized into one convenient method of examining. It should be kept in mind that there are several purposes to the "focal survey:" certain focal deficits (e.g. aphasia) can modify the entire picture of the mental status examination (e.g. falsely suggesting dementia); some focal deficits may be far more disabling than their manifestations in the first portion of the mental status exam might suggest; finally, certain focal deficits as, for example, isolated recent memory deficit, are highly suggestive of specific differential diagnostic lists.

The Prefrontal Areas: loss of one side may be clinically silent; unilateral anosmia due to damage to the olfactory tract may be a clue. Loss or damage to both sides will result in extensive behavioral changes with two main patterns: disinhibition with outbursts of aggression or socially inappropriate behavior, or excessive withdrawal and disinterest, perhaps with otherwise intact cognitive function (e.g. the patient is oriented, can calculate, has a reasonable fund of general information but is incontinent and unconcerned about his illness, etc.).



Dorsal View Cerebral Hemispheres

Figure 1

Damage to lateral premotor areas will result in the apperance of "primitive reflexes" (primarily involuntary grasp and suck responses), increased body tone, and repetitive or perseverative responses to commands. These signs can appear contralateral to the area of damage; in generalized disorders, they appear bilaterally.

Lesions of the motor and sensory strips along the central sulcus result in obvious changes. The earliest signs of hemiparesis are loss of fine motor control and normal postural movements (e.g. normal arm swing when walking) with preservation of power. Unilateral damage to the mesial temporal lobes may be clinically silent, but bilateral damage to this cortex or its subcortical projections (fornices to thalamus) will produce severe deficits in recent memory. This area of cortex is also highly epileptogenic with characteristic types of convulsive manifestations (automatisms, absence attacks, etc.).

The dominant peri-sylvian frontotemporal cortex is tested by the aphasia exam; counterparts on the non-dominant side are clinically silent. Parietal areas of both hemispheres are amenable to bedside testing. Occipital lobes are tested by the visual fields, reading, and visual recognition of people and objects.

Finally, the parasaggital or medial surfaces of the forebrain are evaluated by checking for impaired voluntary sphincter control and the characteristic form of hemiparesis with lower extremity and proximal upper extremity primarily affected. Seizure activity is not uncommon.

Areas represented in white in the diagrams are "silent" in terms of the mental status examinations, though subtle abnormalities may appear in other portions of the neurologic exam.

Conduct of the Focal Survey

An efficient approach: the first step is to establish that the patient is not aphasic or, if he is, that he at least can comprehend commands necessary to complete the examination. Basically, the common aphasias will follow these clinical patterns:

(a) The non-fluent (frontal) aphasic: has a definite hemiparesis; is aware of his deficit and is frustrated; he cannot convey information with speech; comprehension is intact, but production is sparse (non-fluent), dysarthric, and does not obey the rules of simple grammar.

(b) The fluent (temporal) aphasic: is not hemiparetic but may have a homonymous visual field defect; produces fluent speech but this may contain varying amounts of nonsense. Comprehension and naming of common objects are severely impaired.

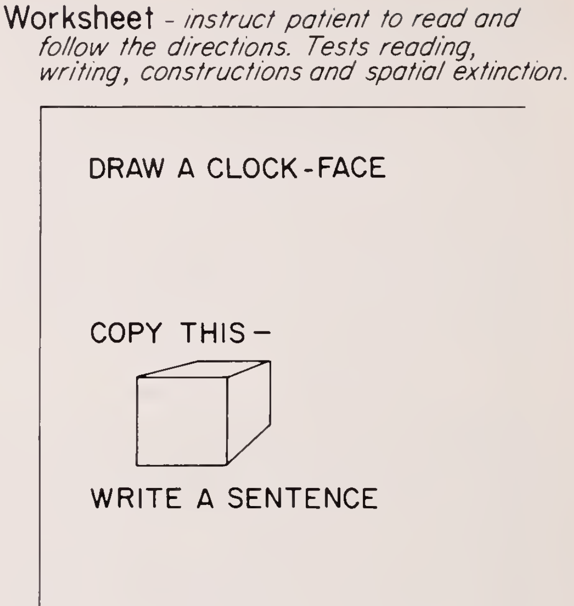
(c) Global aphasia: a massive middle cerebral artery territory lesion; *all* speech functions fail; the patient is hemianopic and hemiparetic. Speech production is virtually nil.

The aphasic patient cannot write much better than he can speak; fluent and some non-fluent aphasics have reading disorders. These rules help in the recognition of psychogenic speech disorders and in distinguishing dysarthria or dysphonia from aphasia.

The actual speech examination may be completed during the history if the patient is normal. If not, classification can be accomplished by testing the naming of common objects, the comprehension of a few commands of increasing complexity, noting speech production and, finally, testing the writing of a simple, unfamiliar sentence.

Next, the patient is given three unrelated words to remember. He repeats them back and is asked for them several minutes later. The interim is filled with other tests to distract him. Normally, all are recalled; two out of three is an equivocal response; recall of fewer items is definitely abnormal. I do not usually test digit span, which really reflects attentiveness and may be reduced by anxiety, nor do I concern myself with "remote memory" since answers are hard to verify. Actually, recent memory deficit, as defined above, is the most clnically relevant form of memory deficit and indicates bilateral dysfunction of the mesial temporal lobes.

While waiting to complete the memory test, parietal lobe function is examined. The dominant parietal lobe is tested by asking the patient to do simple calculations, discriminate right from left (first on himself and then on the examiner), and name common objects. The non-dominant parietal lobe is screened by asking him to copy a three-dimensional figure. History from nursing personnel or the family is essential: can the patient dress himself; can he find his room in his house (testing visuospatial function of non-dominant parietal lobe)? While visual and tactile sensation is being tested, both sides are stimulated simultaneously; a parietal lobe lesion will cause the patient to ignore stimuli on the opposite side of the body when paired with stimulation on the "intact" side. If the patient has normal sesnation in his hads, then graphesthesia (the tactile recognition of traced letters or numbers) may be tested. This fails on the side opposite a parietal lesion.



Worksheet - *instruct patient to read and follow the directions. Tests reading, writing, constructions and spatial extinction.*

DRAW A CLOCK-FACE

COPY THIS –

WRITE A SENTENCE

Figure 2

A work sheet such as that shown in Figure 2 may be given to the patient for efficient assessment of reading comprhension, writing, constructions, and tendency to ignore or extinguish one side of space (perhaps by numbering a clock face only on one side). Completion of the neurologic exam will round out the "survey" of the hemispheres.

Finally, some suggestions for overall approach may be useful: first, explain simply and courteously the purpose of the exam to enlist the patient's cooperation. Confronting an individual with questions such as those in the MSE provokes anxiety and defensiveness. Impaired patients rapidly fatigue; they may at first respond slowly and then, not at all. Therefore, intersperse your mental status exam with other parts of the physical and neurologic exam and do those items essential to your assessment first. Recognize the patient's limitations: the severely demented patient, for example, often can be identified early in the general survey, at which point further redundant testing can be discarded. Go, instead, to a screen for focal disesae. *Irritation on the part of the physician during an interview or physical exam with any patient should raise the possibility that the patient cannot follow commands or answer questions precisely; perhaps the mental status examination should be performed.*

Further details on the conduct of these and other tests of mental status are discussed in a recently available monograph[1].

Examples

Example 1

A 68-year-old hypertensive male patient, referred for evaluation of confusion and irritability: the general survey reveals an unkempt man without insight who irritably refuses examination. Mood quickly shifts to jocularity; thought is extremely tangential and wanders from topic to topic. He is quite angry and suspicious about his last physician. He denies hallucinations. He eats well, has difficulty getting to sleep but remains asleep throughout the night. Primitive reflexes are present. Focal survey is unremarkable. IMPPRESION: The lability of mood, paranoid ideation, tangentiality of thought, lack of insight, and the presence of primitive reflexes combine to suggest organic brain syndrome. Strong evidence for depression is lacking with no consistent depressive mood tone and none of the vegetative symptoms of depression.

Example 2

The patient is a 45-year-old alcoholic, referred for evaluation of confusion. The general survey reveals a pleasant, appropriate man with no insight into his problem. He is well kempt; thought processes and content are intact. He is disoriented. Focal survey reveals a normal digit span but marked impairment of recent memory with the patient able to remember zero of three items after five minutes and only three of 14 items in a short story on immediate repetition. Canfabulation is present. IMPRESSION: Amnestic syndrome of unknown etiology, most likely Korsakoff's psychosis.

Example 3

This 65-year-old woman is referred for evaluation of headache. General survey reveals a neatly dressed, alert woman, complaining of headache but denying other difficulties. She is oriented; thought content and progression are normal. Affect is pleasant to mildly euphoric with no lability. Focal survey reveals left sensory extinction, left agraphesthesia, constructional apraxia. IMPRESSION: Right parietal lesion with associated anosognosia (i.e. unawareness of illness or disability). General mental status is intact except that the patient's mood and affect are inappropriate for her situation; i.e. more concern and anxiety would be expected from the average patient.

Example 4

A 50-year-old woman is referred for evaluation of urinary and fecal incontinence. General survey reveals an inattentive but alert woman with no apparent insight or concern about her problem. Thought content is restricted, and she answers questions with a single word or phrase. Primitive reflexes are present. Other cognitive functions tested in the focal survey are intact. IMPRESSION: This patient has a rather advanced frontal lobe syndrome such as might be seen with a frontal neoplasm. Earlier in her course, she may merely have seemed inattentive and may well have irritated her physician and others by failing to attend to and follow commands.

Example 5

A 74-year-old man is referred for lethargy and confusion. The patient is disheveled, inattentive, yawning, and tending to drift off to sleep. At this point, the general survey can be terminated with the recognition of patient's impaired level of consciousness. The examiner now performs an abbreviated focal survey, remembering that the patient is likely to rapidly fatigue and become less responsive as time goes on. The focal survey can begin with visual fields, an attempt to get the patient to speak and follow simple commands, and then, if possible such things as sensory extinction. The patient is most unlikely to be attentive enough to do things such as graphesthesia or accurate memory testing. The work up is predominantly guided by his impaired level of consciousness. Coma examination and analysis should distinguish infratentorial, supratentorial, or metabolic cause of coma.

Example 6

A 72-year-old man, referred for evaluation of confusion: the patient was post-operative TURP. Abnormal behavior consisted of attempting to remove his own Foley catheter and wandering about the nursing unit, getting into the wrong bed. The general survey reveals a disoriented, disheveled man with flat affect, no insight, and a tendency to perseverate. The general survey need not proceed beyond this as the data is adequate to identify abnormal thought and affect of psychotic proportions. Etiology is organic in view of dishevelment, disorganized behavior, disorientation, and lack of insight and perseveration (a frontal lobe sign). Focal survey can begin and, in this man, reveals primitive reflexes but no localizing signs. IMPRESSION: The definite organic brain syndrome without focal abnormalities suggests a diffuse etiology (i.e. metabolic, epileptic, or degenerative) rather than a focal process (subdural hematoma, infarction, etc.). If a history were obtainable, it might be found that the patient's mental state had been impaired prior to surgery, thus helping to rule out an acute metabolic encephalopathy or intra-operative hypoxic event as the basis for his behavior.

Reference

1. Black F. William, Strub Richard L: The Mental Status Examination in Neurology. Philadelphia, F.A. Davis Company, 1977.

Continuing Medical Education

St. Paul Ramsey Medical Center

The first *CLINICAL TOXICOLOGY* quarterly update conference will be held in the Amphitheater at St. Paul-Ramsey Medical Center on January 9, 1980. Guest speaker will be Dr. Barry Rumack, Director of the Rocky Mountain Poison Center, Denver General Hospital, Denver, Colorado. The subject of his talk will be "Acetaminophen Poisoning".

These conferences qualify for Category I CME credits and are sponsored by the Emergency Medicine Department at St. Paul-Ramsey Medical Center and the University of Minnesota Medical School under the direction of Dr. Kusum Saxena. Contact: Carol Wolf at (612) 221-3311.

(Continued from page 894)

FAMILY PRACTITIONER, OB-GYN, orthopedic surgeon to join incorporated seven man group in central Minnesota; 120 bed hospital. Lake area, excellent leisure activities. Starting salaries: family practitioner $40,000 per year; ob-gyn $50,000 per year; orthopedic surgeon $70,000 per year. Contact personnel director, Little Falls Clinic, Little Falls, Minnesota. Telephone 612/632-3611

THE FARIBAULT CLINIC. LTD., has an opening for a Family Physician. The Clinic is in a rural community near the Metropolitan area and has seven Family Physicians, two Surgeons and two Internists. The Clinic has just completed a remodeling and expansion program. For more information please write to: Darral Mischke, Administrator, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

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FAMILY PRACTICE SUBURBAN MINNEAPOLIS Private practice opportunity with established group near modern accredited hospital. Must be Board Eligible or Board Certified and do OB. No weekend call. Excellent referral centers and continuing medical education in adjacent city. Family oriented suburban location. Reply with curriculum vitae in confidence to MINNESOTA MEDICINE (549), 101 East 5th St., #900 St. Paul, Minnesota, 55101.

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G.P. OR F.P. needed to continue practice from which I wish to retire. 100 Bed Hospital. Excellent consultants. Best little city of 17,000 in State. D. J. Studer, M.D., Faribault, MN. 55021. Tel: 507-334-5960.

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FAMILY PHYSICIAN to join two Board-Certified family doctors, one physicians assistant, and one family counselor in a young and growing medical practice in beautiful Central Minnesota. The practice is oriented towards holistic medicine with a commitment to patient and community education. 80 minutes to downtown Minneapolis. Cultural and recreational activities in abundance. Salary range $35-43,000 depending on qualifications. Contact Adm. Douglas F. Adamek or Thomas J. Newton, M.D. at Cold Spring Medical Clinic, 26 N. Red River Ave., Cold Spring, MN 56320 — 612-685-8641.

THE MIDELFORT CLINIC is seeking associates in the following areas: Family Practice, Cardiology, Allergy, This is an opportunity to affiliate with a 48 member group located in a college community of 50,000. Satellite practice locations also available. Contact G. E. Owen, M.D., Midelfort Clinic, Ltd., Eau Claire, WI 54701 or call 715/839-5222.

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EXCELLENT OPPORTUNITY for two or three family practitioners in small, stable economic community serving 15,000 population. Move into a new clinic attached to 38 bed, well equipped JCAH accredited hospital. One physician now working in the four man clinic. No investment is necessary and you'll be guaranteed a liberal salary with many fringes. Enjoy the many advantages of small community living while living in an area that offers diversified recreational activities, excellent schools and a warm environment. Write or call Omer Eischens, Hospital Administrator, Tracy Municipal Hospital, Tracy, Mn. 56175. Phone collect: 507-629-3200.

OUTSTANDING OPPORTUNITY for two family physicians to join young group of six, Board certified family physicians, one general surgeon who is a fellow of the American College of Surgery, one physician's assistant and one Ph.D. family counselor. The new 11,000 square foot clinic is located just Southwest of the Minneapolis metropolitan area and offers excellent access to the downtown area while offering the advantages of small-town living. The Shakopee area also possesses an outstanding school system. In the Summer of 1980, it is anticipated that an 8,000 square foot expansion will be completed by the clinic and will be located in Prior Lake, Minnesota. Both the clinics will be serviced by St. Francis Hospital (126 bed, full-service facility). The Shakopee Medical Center offers early buy-in possibilities and excellent fringe benefits. For further information contact Donald Lynch, M.D. or David C. Fleming, Clinic Administrator at the Shakopee Medical Center, 1335 East Tenth Avenue, Shakopee, MN, 55379 or phone 612-445-1305.

75 MINUTES FROM Minneapolis. Group of four Family Physicians wants to add a surgeon and another Family Physician. Beautiful city with lakes + parks. Incorporated group which stresses family life and free time. *HEW designated physician shortage area*. Minnesota Medicine, (548) 101 E. 5th St., #900, St. Paul, MN, 55101.

ENDOSCOPIST/GASTROENTEROLOGIST or internist with sub specialty in gastroenterology and endoscopy, to join young family practice group of 9 family physicians and a general surgeon. Contact: Peter A. Setness, M.D. Doctors' Clinic, LTD. 121 S.E. 11th Ave. Forest Lake, MN (612) 464-7100.

ANESTHESIOLOGIST needed in outstate Minnesota. Should be board certified or eligible. Department has 300+ cases per month. Malpractice insurance paid. $60,000 first year, then buy in. Write: Minnesota Medicine — 547, Suite 900, 101 E. 5th St., St. Paul 55101.

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FOR SALE: Quinton Treadmill, Tektronix Oscilloscope, Medilog Monitor, Corning Flame photometer and miscellaneous office equipment. Please call Beryl Lee at 738-2088.

PRIMARY CARE PHYSICIAN NEEDED AT TWO Minnesota correctional institutions close to the Twin Cities area. Fully equipped and professionally staffed ambulatory care facilities. Inpatient care provided at community hospitals. Maintain close association with health administrator in Central Office to continue a very progressive, quality oriented service delivery system. Employed through St. Paul Ramsey Medical Ctr. with contract responsibilities to Department of Corrections. Very competitive salary with opportunity for outside practice, faculty position at Univ. of Minn. with staff membership at two major teaching hospitals plus other generous and unusual benefits. Contact: Howard L. Johnson, MHA, Health Care Administrator, Minnesota Department of Corrections, 430 Metro Square Bldg., St. Paul, Minn. 55101 Phone (612) 296-2157.

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(Continued to page 908)

(Continued from page 907)

Medical Doctors — Consider an employment situation that offers: a competitive salary, a 40-hour week, malpractice coverage, 30 days paid vacation, and other excellent fringe benefits, in a JCAH accredited progressive medical center. The City of St. Cloud and the surrounding area boasts of the high quality of family living that is afforded its residents, who enjoy clean air, easy access to a wide variety of four-season outdoor recreational opportunities, excellent educational facilities which include a State University, St. John's University and the College of St. Benedict and a full range of services available in a metropolitan setting while maintaining the quality of suburban and rural living. License in any state accepted. Current and anticipated opportunities are in Psychiatry, Internal and General Medicine. Financial assistance to defer cost of relocation. Equal Opportunity Employer. Write: Chief of Staff, Veterans Administration Medical Center, St. Cloud, Minnesota 56301, or call the Personnel Service (612) 252-1670.

Wanted: 1, 2, or 3 PHYSICIANS for partially equipped Doctors Building in Buffalo, Minnesota, 30 miles west of Minneapolis. Contact Herbert Winge, M.D., 1311 Viking Drive, Buffalo, MN 55313. Or telephone 1-612-682-4881 on weekends.

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Office space — share large, well decorated suite in Minneapolis Medical Arts Bldg. 1 or 2 rooms plus shared reception room. Secretarial, bookkeeping, lab. and chest x ray services available on cooperative basis if desired. 333-1531.

Ob-gyn: Ten man group with two OB-GYN's seeks another OB-GYN partner. Attractive offer now with promising future. Send C.V. We will call. Gordon Rock, M.D., The Davenport Clinic, 1820 West Third Street, Davenport, Iowa 52802.

Wanted: General Surgeon, board certified or eligible, to join seven man family practice group in a University town with trade area population of 22,000, 30 miles southeast of St. Paul, MN JCAH approved hospital. Contact Roland M. Hammer, M.D., River Falls Medical Clinic, Ltd., River Falls, Wisconsin, 54022, or call collect (715) 425-6701.

Experienced general surgeon needed to join two general internists, a gastroenterologist, four family practitioners and a pediatrician in a busy Satellite of the Marshfield Clinic at Ladysmith, Wisconsin. Complete details and personal interview will be arranged for qualified applicants. Send curriculum vitae, bibliography and three references to William M. Toyama, M.D., Department of Surgery, Marshfield Clinic, 1000 N. Oak Avenue, Marshfield, Wisconsin 54449.

Internist — cardiologist in practice seeking part time job 4-5h a day and some weekends or 2-3 full days. Call 925-4038, 10a.m.-1:00p.m. Dr. Galperin.

Ob-gyn associate wanted by board certified OB-GYN in Little Falls, Mn. Equal sharing of surgery and OB the first year with negotiable salary and full partnership in a multispecialty group after. Pref. Amer. Tr. Must be board eligible or certified. Contact J. M. Doty, MD, FACOG, Little Falls, Mn. 612-632-6611.

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VOLUME 62 INDEX

JANUARY — DECEMBER, 1979

A

Aadalen, Richard J.: Proximal Tibial Metaphyseal Fractures in Children. A Complication. 785
Abuzzahab, F.S., Sr.: Twenty-five Years of Psychopharmacology. 79
Abuzzahab, F.S., Sr.: 25 Years of Psychopharmacology. Special Issue — Part II. 574
Achalasia of the Ureter. Michael Bjork, 649
Acute Lymphoblastic Leukemia of Childhood. Peter F. Coccia and Mark E. Nesbit, Jr., 527
Acute Non-Lymphocytic Leukemia. Clara D. Bloomfield, 529
Acute Non-Lymphocytic Leukemia in Elderly Patients. Bruce A. Peterson, 531
Acute Viral Myocarditis. Clinical and Histologic Changes. C. M. Bandt, N. A. Staley and G. R. Noren, 234
Adjuvant Chemotherapy for Large Bowel Cancer. An Optimistic Appraisal. Theodor B. Grage, 511
Adjuvant Chemotherapy of Breast Cancer. B. J. Kennedy, 509
Adjuvant Therapy of Malignant Melanoma. Gerald J. Vosika, 515
Advanced Breast Cancer. Current Therapy. David T. Kiang, 521
Advanced Ovarian Cancer. B. J. Kennedy, 525
Advanced Testis Cancer. B. J. Kennedy, 523
Advances in Oral-Facial Deformity Reconstruction. Franklin R. Stickel, Tague C. Chisholm, David D. Benson, 405
Alkon, Ellen and Carlson, Gertrude: Low Birth Weight Births to Girls Enrolled in the Minneapolis Pregnant School Girl Program. 822
American Diabetes Association. David L. Zuelke, 55
An Adult Phenylketonuric with Schizophrenia. Clinical and Biochemical Similarities and Possible Genetic Connection between the Two Diseases. Robert O. Fisch, William B. Hosfield, Pi-Nian Chang, John Barranger, and Donald W. Hastings, 243
An Efficient Approach to the Mental Status Examination. Bruce D. Snyder, 901
Anderegg, Alfred F.: HMOs — Their Limitations and Role, 797
Anderson, Lowell J.: Physicians, Pharmacists and Refills. 615
Anterior Cranial Vault and Bony Orbit in Infancy. Craniofacial Surgery. Bruce B. Shilling, Erich S. Wisiol, Brooks J. Poley, and Thomas W. Purcell, 399
Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage. Kenton Bodily and Ronald P. Fischer, 225
Appendicovesical Fistula. Culley C. Carson III and Reza S. Malek, 773
Arthroscopy of the Knee. Another Diagnostic Technique. James D. Priest, 710
Asinger, Richard W., Strauss, William E., Hodges, Morrison, Rourke, Terry and Helseth, Hovald K.: Left Atrial Myxoma Presenting as Shock. Diagnosis by Echocardiography, 723
Asphyxia and Resuscitation. Roderick Krueger, 201
Atopic Dermatitis Associated with Citric and Malic Acid Intolerance. William E. Walsh, 637
Aufderheide, Arthur C.: RH Isoimmunization Prevention Program in a Community Hospital. 181

B

B & T Markers in Leukemia and Lymphoma. Clara D. Bloomfield, 499
Baker, A. B.: Vertigo. 60
Bandt, C. M., Staley, N. A. and Noren, G. R.: Acute Viral Myocarditis. Clinical and Histologic Changes. 234
Bendel, Richard P.: Prenatal Detection of Genetic Diseases. 135
Bendel Richard P.: Management of Labor in the High-Risk Patient. 133
Bjork, Michael: Achalasia of the Ureter. 649
Bloomfield, Clara D.: Acute Non-Lymphocytic Leukemia. 529
Bloomfield, Clara D.: B & T Markers in Leukemia and Lymphoma. 499
Bloomfield, Clara D.: Non-Hodgkin's Malignant Lymphoma. 533
Bodily, Kenton and Fischer, Ronald P.: Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage. 225
Bosl, George J.: Chorionic Gonadotrophin and Alpha-Fetoprotein Markers for Testicular Cancer. 507
Bosl, George J. and Edson, J. Roger: Intravascular Coagulation. 544
Brainard, John B.: Post-Operative Headache. A Manageable Complication. 247
Breitenbucher, R. B.: Detection and Chemo Prophylaxis of Tuberculosis in Southeast Asian Immigrants. 805
Briggs, Thomas G.: General Management Guideline for the Alcoholic and Other Chemically Dependent. 176
Brown, David R. and Uden, Donald L.: The Use of 1-desamino-8-D-arginine Vasopressin (DDAVP) in the Management of Neurogenic Diabetes Insipidus. (Multiple Etiologies in Pediatric Patients). 427
Burns, John M. and Hamlon, John S.: Minnesota "Brain Death" Legislation: A Step Forward . . . or Backward? 273 and 363

C

Cabanela, Miguel E. and Johnson, Kenneth A.: Injuries of the Lower Cervical Spine. 351
Cadaver Kidney Transplantation. Effect of Hypotension and Donor Pretreatment with Methylprednisolone and Phenoxybenzamine. Luis H. Toledo-Pereyra, Richard L. Simmons, Leslie C. Olson and John S. Najarian, 159
Cain, J. C.: Continuing Medical Education. 85
Campaigne, R. J.: Malignancy of the Ovary. 360
Cardiovascular System and Dizziness. Robert Van Tassel. 63
Carryer, Haddon: Robert T. Kelly. 395
Carson, Culley C. III and Malek, Reza S.: Appendicovesical Fistula. 773
Case for "Brain Death" Legislation. A Response to the Critics. William H. Manning and Howard J. Vogel, 121
Cataract Surgery. Committee on Ophthalmology. 759
Cerebral Tuberculoma. John R. Mawk, Mahmoud G. Naguib, Jesse C. Yap and Shelley N. Chou, 331
Chlorpromazine's Entrance into Psychiatry. An Extremely Interesting Product. Judith P. Swazey, 81
Cholelithiasis in a Child without Hemolytic Anemia. Michael J. Weiner, 223
Cholestasis of Pregnancy. Donald S. Mattson and Gregory M. Olson, 261

C (continued)

Chorionic Gonadotrophin and Alpha-Fetoprotein Markers for Testicular Cancer. George J. Bosl, 507
Coccia, Peter F. and Nesbit, Mark E., Jr.: Acute Lymphoblastic Leukemia of Childhood. 527
Cohan, Richard C.: Legal and Ethical Aspects of Pre-Employment Physical Examinations. 799
Colposcopy Experience at St. Louis Park Medical Center. Arlyn A. Hamann, 283
Colton, Roger: Natural Course of Rheumatoid Arthritis. 129
Congenital Factor VII Deficiency. Safety of Surgery without Preoperative Transfusion. R. D. Niedringhaus, Johannes Aas, and J. B. Sanford, 791
Continuing Medical Education. Q and A — CME. J. C. Cain, 85
Control and Cure of Cancer. B. J. Kennedy, 487
Corbett, Lionel: Impact of Depot Neuroleptics on Psychiatry. 97
Cotton, G. E. and Sill, A. J.: Insulin Therapy. Things That Make a Difference. 31
Court Decision on United States vs. American Society of Anesthesiologists. Charles A. Geer, 855
Cultural Aspects in Working with Lao Refugees. Karen Olness, 871
Cunningham, Bruce L., Shaw, William W., Mayfield, Jack K. and Shons, Alan R.: Free Flap Reconstruction of the Lower Extremity. 707

D

Davis, John M. and Dysken, Maurice W.: Impact of Psychotropic Drugs on Research in Psychiatry. 109
Davis, Michael W. and Litman, Thomas: Figure Skater's Foot. 647
Dean, Andrew G.: Suggestions for Medical Screening of Southeast Asian Refugees. 753
DeMartini, David R., Plucker, Milton W., Johnson, Frank and Gobel, Fredarick L.: Ergot Induced Unilateral Brachial Arterial Occlusion. 719
Detection and Chemo Prophylaxis of Tuberculosis in Southeast Asian Immigrants. R. B. Breitenbucher, 805
Devney, Robert and ten Bensel, Robert W.: Television and Children. A Physician's Guide. 833
Diagnosis of Acute Knee Injuries. James D. Priest, 657
Diagnosis of Rheumatoid Arthritis. James Reinertsen, 185
Diagnostic Uses of Anorectal Manometry in Pediatrics. Felix A. McParland and Karen Olness, 447
Dizziness. Melvin E. Sigel, 59
Drake, R. M. and Franciosi, R. A.: Fetal Turner Syndrome. 443
Drugs and Depression. Tools and Treatments. Leo E. Hollister, 589
D-Penicillamine in Treatment of Rheumatoid Arthritis. Charles H. McKenna, 875

E

Enucleating Donor Eyes and Uses of Donor Eyes. Ronald Linde, 153
Ergot Induced Unilateral Brachial Arterial Occlusion. David R. DeMartini, Milton W. Plucker, Frank Johnson and Fredarick L. Gobel, 719
Estrogen Receptors in Breast Cancer. David T. Kiang, 497
Ewing's Sarcoma. Mark E. Nesbit, Jr. 513
Experience with Colonoscopic Polypectomy. Review of 700 Polyps. Santhat Nivatvongs and Stanley M. Goldberg, 197
Extra-Articular Manifestations of Rheumatoid Arthritis. H. S. Luthra, 743

EDITORIALS

Abuzzahab, F. S.: Twenty-five Years of Psychopharmacology. 79
Agustsson, Hreidar: RH Isoimmunization. 175
Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage. Joseph C. Kiser, 257
Arey, Stuart Lane: Cholelithiasis in a Child without Hemolytic Anemia. 253
Beriou, Judy M. and Fylling, Carelyn: Team Management of the Diabetic Patient. 11
Brown, David Raoul: 1979- Beyond Forgiveness? 397
Cholelithiasis in a Child without Hemolytic Anemia. Stuart Lane Arey, 253
Cholestasis of Pregnancy. William C. Meyer, 255
Colonoscopic Polypectomy and Beyond. Frederic D. Nemer, 171
Diabetes Mellitus. Past, Present and Future. Leonard Mastbaum, 9
Farley, Harrison H.: Intestinal Fistula from A Toothpick. 337
Fruition of a Dream. Daniel J. Whitlock, 398
Intestinal Fistula from A Toothpick. Harrison H. Farley, 337
Kiser, Joseph C.: Aortic Rupture and Right Ventricular Rupture Induced by Closed Chest Cardiac Massage. 257
Malignancy of the Ovary. Konald Prem, 335
Mastbaum, Leonard: Diabetes Mellitus. Past, Present and Future. 9
Meyer, Charles R.: Mononuclear Infiltrates in the Myocardium. 253
Meyer, William C.: Cholestasis of Pregnancy. 255
Micropolycystic Liver and Gluten Sensitivity — So What? C. A. Pierach, 255
Mononuclear Infiltrates in the Myocardium. Charles R. Meyer, 253
Nemer, Frederic D.: Colonoscopic Polypectomy and Beyond. 171
1979 — Beyond Forgiveness? David Raoul Brown, 397
Pierach, C. A.: Micropolycystic Liver and Gluten Sensitivity — So What? 255
Phenylbutazone-Induced Hepatitis. Joseph M. Tombers, 337
Prem, Konald: Malignancy of the Ovary. 335
RH Isoimmunization. Hreidar Agustsson, 175
Strom, Gordon W.: Urologic Ski Injuries. 175
Team Management of the Diabetic Patient. Judy M. Beriou and Carelyn P. Fylling, 11
Tombers, Joseph M.: Phenylbutazone-Induced Hepatitis. 337
Twenty-five Years of Psychopharmacology. F. S. Abuzzahab, Sr., 79
Urologic Ski Injuries. Gordon W. Strom, 175
Whitlock, Daniel J.: The Fruition of a Dream. 398

EDITOR'S NOTEBOOK

Reece, Richard L.:
  All Things Considered (September) 631
  Editor's Report to the House of Delegates (May) 317
  Hospital Solvency and Hospital Marketing (October) 703
  How to Avoid Running: or, Time-Consuming Exercises for Non-Runners (July) 479
  MINNESOTA MEDICINE: The Long and Short of It (January 7
  Postcards from Dubrovnik, London, and Lonsdale (March) 147
  ". . . power, finances, and government, and rather less about the humanistic aspects of medicine." (June) 391
  Slanted views (August) 573
  thrrree rrrs (February) 77
  United States Health Care System — The Next Ten Years: Government Regulation, Private Competition, or Something In-between? (April) 219

F

Farewell Old QACME. J. S. Welch. 137
Febrile Convulsions. Current Controversies. John T. MacDonald, 433
Feinberg, Samuel: Use of Imaging Techniques in Cancer Diagnosis. 489
Fenger, Thomas A.: Role of Prospective Medicine in Health Care. 841
Ferguson, Richard H.: Malignant Disease and Rheumatism. 551
Fetal Turner Syndrome. R. M. Drake and R. A. Franciosi, 443
Figure Skater's Foot. Michael W. Davis and Thomas Litman, 647
Fisch, Robert O., Hosfield, William B., Chang, Pi-Nian, Barranger, John, and Hastings, Donald W.: An Adult Phenylketonuric with Schizophrenia. Clinical and Biochemical Similarities and Possible Genetic Connection between the Two Diseases. 243
Food and Drug Administration Regulation of Clinical Psychopharmacology. Burtrum C. Schiele, 593
Franciosi, Ralph A.: Infant at Risk for Early Onset Group B Streptococcal Infection. 801
Franz, Marion: Nutritional Management in Diabetes. 41
Free Flap Reconstruction of the Lower Extremity. Bruce L. Cunningham, William W. Shaw, Jack K. Mayfield, and Alan R. Shons, 707
Frenning, Daniel H.: Hypercalcemia in Neoplastic Diseases. 541
Future of Psychopharmacology. Nathan S. Kline, 599

G

Gallagher, Rollin M.: The Impact of Benzodiazepines on Clinical Practice. Considerations for Therapeutic Use. 580
Gaziano, Emanuel P. and Freeman, Donald W.: Intrapartum Fetal Heart Rate Monitoring. Review of Recent Experience. 737
Geer, Charles A.: Court Decision on United States vs. American Society of Anesthesiologists. 855
General Management Guideline for the Alcoholic and Other Chemically Dependent. Thomas G. Briggs, 176
Genetic Aspects of Diabetes Mellitus. Richard A. King and Jose J. Barbosa, 14
Gerich, John E.: Potential Future Modes of Therapy in Diabetes Mellitus. 46
Gilbert, Howard D.: Ocular Changes in Diabetes. 22
Grage, Theodor B.: Adjuvant Chemotherapy for Large Bowel Cancer. An Optimistic Appraisal. 511

H

Hamann, Arlyn A.: Colposcopy Experience at St. Louis Park Medical Center. 283
Hamlon, John S. and Burns, John M.: Minnesota "Brain Death" Legislation: A Step Forward . . . Or Backward? 273 and 363
Harris, Michael A.: Shock Lung: An Overview. 727
Health Care Problems among the Southeast Asian Refugees. "The Boat People." Neal R. Holtan, 633
Heid, James K.: RPAP — A Boon to Rural Minnesota. 826
Henke, Clarence E., Wolff, John M. and Shafer, Rex B.: Scintiangiographic Identification of Lesion Producing Foix-Alajouanine Syndrome. 653
Hick, John F.: Preschool Screening: Right or Ritual? 373
Hildreth, T. A., Cass, A. S. and Khan, A. U.: Skiing Injuries to the Urinary Tract. 155
HMOs — Their Limitations and Role. Alfred F. Anderegg, 797
Hodge, David S., Comty, Christiana M. and Helseth, Hovald K.: Surgical Treatment of Uremic Pericarditis. 323
Hoffman, Neil R.: Liver Injury Secondary to Radiation Therapy for Breast Cancer. 778
Hollister, Leo E.: Drugs and Depression. Tools and Treatments. 589
Holtan, Neal R.: Health Care Problems among the Southeast Asian Refugees. "The Boat People." 633
Holtan, Neal R., Crossley, Kent B. and Pries, Constance N.: Prevalence of Intestinal Parasites in a Laotian Immigrant Community. 749
Hui, Frank C., Coventry, Mark B., Veasy, George D. and Cabanela, Miguel E.: Treatment of Ununited Fractures Adjacent to Joints. 895
Hypercalcemia in Neoplastic Diseases. Daniel H. Frenning, 541

HEALTH CARE COST COMMISSION

Frey, Richard J.: (May) 315, (July) 553
Physicians Act on Cost Commission Report (July) 555
Report and Recommendations of the Minnesota Medical Association's Commission on Health Care Costs 1979. Supplement to May issue

I

Idiopathic Thrombocytopenic Purpura in Childhood. Lawrence J. Singher, 455
Immunotherapy in Cancer. Current Status and Future Prospects. Gerald Vosika, 549
Impact of Benzodiazepines on Clinical Practice. Considerations for Therapeutic Use. Rollin M. Gallagher, III, 580
Impact of Depot Neuroleptics on Psychiatry. Lionel Corbett, 97
Impact of Psychotropic Drugs on Research in Psychiatry. John M. Davis and Maurice W. Dysken, 109
Infant at Risk for Early Onset Group B Streptococcal Infection. Ralph A. Franciosi, 801
Infanticide. A Historical Perspective. Beverly A. Montag and Thomas W. Montag, 368
Injuries of the Lower Cervical Spine, Miguel E. Cabanela and Kenneth A. Johnson, 351
Insulin Therapy. Things That Make a Difference. G. E. Cotton and A. J. Sill, 31
Intestinal Fistula from A Toothpick. Peter A. Jernigan and Gerald T. Mullin, Jr. 321
Intrapartum Fetal Heart Rate Monitoring. Review of Recent Experience. Emanuel P. Gaziano and Donald W. Freeman, 737
Intravascular Coagulation. George J. Bosl and J. Roger Edson, 544
Investigational New Drugs in Cancer Chemotherapy. Bruce A. Peterson and Kathleen Briscoe, 536

J

Jernigan, Peter A. and Mullin, Gerald T., Jr.: Intestinal Fistula from A Toothpick. 321
Johnson, George Magnus and Johnson, Janice B.: Living with Diabetic Children. A Family Affair. 51
Jones, Miles J. and Siegal, Gene P.: Testicular Surprises in Two Apparently Healthy Young Men. 671
Juvenile Rheumatoid Arthritis. H. D. Venters. 463

K

Kaplan, Lawrence R. (Editor: Robert J. McCollister): Laparoscopy in Internal Medicine. 899
Katkov, Harold: Pediatric Cardiology at Children's Health Center. First Five Years. 411

K (continued)

Kelly, Robert T.: Haddon Carryer, 395
Kennedy, B. J.: Adjuvant Chemotherapy of Breast Cancer. 509
Kennedy, B. J.: Advanced Ovarian Cancer. 525
Kennedy, B. J.: Advanced Testis Cancer. 523
Kennedy, B. J.: Control and Cure of Cancer. 487
Key, Jack D.: Thomas E. Keys, Medical Librarian, Historian, Scholar, and Author-Extraordinarius. 883
Thomas E. Keys. Medical Librarian, Historian, Scholar, and Author-Extraordinarius. Jack D. Key, 883
Kiang, David T.: Advanced Breast Cancer. Current Therapy. 521
Kiang, David T.: Estrogen Receptors in Breast Cancer. 497
King, Richard A. and Barbosa, Jose J.: Genetic Aspects of Diabetes Mellitus. 14
Klain, David B. and Knox, G. Eric: Meconium Aspiration Syndrome. Treatment of the Clinical Problem. 417
Kline, Nathan S.: Future of Psychopharmacology. 599
Krueger, Roderick: Asphyxia and Resuscitation. 201
Kyle, Richard F. and Gustilo, Ramon B.: Necrotizing Fasciitis. A Lethal Infection. 775

L

Laboratory Evaluation of Thyroid Function. Michael W. Steffes and Jack H. Oppenheimer, 162
Laparoscopy in Internal Medicine. Lawrence R. Kaplan. Editor: Robert J. McCollister, 889
Larson, Theodore G.: Limbitrol — A Medical Dream or Nightmare. 725
Lateral Decubitus Radiograph of the Chest in Pediatric Radiology. An Additional Use. Leland H. Prewitt, Jr. and Shashikant M. Sane, 423
Left Atrial Myxoma Presenting as Shock. Diagnosis by Echocardiography. Richard W. Asinger, William E. Strauss, Morrison Hodges, Terry Rourke, and Hovald K. Helseth, 723
Legal and Ethical Aspects of Pre-Employment Physical Examinations. Richard C. Cohan, 799
Limbitrol — A Medical Dream or Nightmare. Theodore G. Larson, 725
Linde, Ronald: Enucleating Donor Eyes and Uses of Donor Eyes. 153
Liver Injury Secondary to Radiation Therapy for Breast Cancer. Neil R. Hoffman, 778
Living with Diabetic Children. A Family Affair. George Magnus Johnson and Janice B. Johnson, 51
Loken, Merle K. and Frick, Mathis P.: Role of Nuclear Medicine in Oncology. 491
Low Birth Weight Births to Girls Enrolled in the Minneapolis Pregnant School Girl Program. Ellen Alkon and Gertrude Carlson, 822
Lung Cancer. Current Evaluation and Therapy. Gerald Vosika, 519
Lung Cancer Patients Treated with Corynebacterium Parvum. Phase I Toxicity Study. Richard YaDeau, Henry A. Bates and Ignacio Fortuny, 673
Luthra, H.S.: Extra-Articular Manifestations of Rheumatoid Arthritis. 743

LETTERS TO THE EDITOR

Anderson, Brian: Health Care Cost Commission. 611
Buselmeier, T. J.: Uremic Pericarditis. 669
Cain, J. C.: Senior Citizen Retired Physician. 667
Klein, William J., Jr.: U.S. Health Care System. 668
Walker, H. Charles Jr., Frick, Mathis P., Feinberg, Samuel B., Gedgaudas, Eugene: The Barium Enema: Is It Alive? 259

M

MacDonald, John T.: Febrile Convulsions. Current Controversies. 433
Malignant Disease and Rheumatism. Richard H. Ferguson, 551
Malignancy of the Ovary. R. J. Campaigne, 360
Management of Labor in the High-Risk Patient. Richard P. Bendel, 133
Manning, William H. and Vogel, Howard J.: The Case for "Brain Death" Legislation. A Response to the Critics. 121
Mattson, Donald S. and Olson, Gregory M.: Cholestasis of Pregnancy. 261
Mawk, John R., Naguib, Mahmoud G., Yap, Jesse C. and Chou, Shelley N.: Cerebral Tuberculoma. 331
Mayer, Thomas R.: Phenylbutazone-Induced Hepatitis. 349
Mayne, John G.: Planning A Treatment Program for the Patient with Rheumatoid Arthritis. 250
McKenna, Charles H.: D-Penicillamine in the Treatment of Rheumatoid Arthritis. 875
McParland, Felix A. and Olness, Karen: Diagnostic Uses of Anorectal Manometry in Pediatrics. 447
Meconium Aspiration Syndrome. Treatment of the Clinical Problem. David B. Klain and G. Eric Knox, 417
Metropolitan Medical Office BuildingFire. The Event and its Consequences. David L. Moody and Jim Thalhuber, 279
Micropolycystic Liver Occurring in an Adult with Gluten Enteropathy. C. E. Weigent and K. C. Hanson, 231
Minnesota "Brain Death" Legislation: A Step Forward . . . or Backward? John M. Burns and John S. Hamlon, 273 and 363
Misconceptions about Possibly Rabid Animals that Have Bitten Humans. Michael R. Peterson and Barry S. Levy, 266
Montag, Beverly A. and Montag, Thomas W.: Infanticide. A Historical Perspective. 368
Moody, David L. and Thalhuber, Jim: Metropolitan Medical Office Building Fire. The Event and its Consequences. 279

MINNESOTA MEDICINE

Minnesota Medicine's Best of the Year (May) 339

MINNESOTA MEDICAL ASSOCIATION

Committee on Ophthalmology: Cataract Surgery (October) 759
Fifty Years of Faithful Service, 1979 Fifty Club (May) 341
MINNPAC Helps Your Practice of Medicine, L. Ashley Whitesell, Jr., (July) 508
Report of Nominating Committee (May) 343
Thorson, S.V.:
  MMA Annual Meeting, May 17-18, St. Paul. (January) 64 (February) 80, (March) 156, (April) 289
Your Doctor Is Worried Too (Standup placard) April) 287
Woellner, Richard C.: D-Day 1980. 856

N

Natural Course of Rheumatoid Arthritis. Roger Colton, 129
Necrotizing Fasciitis. A Lethal Infection. Richard F. Kyle and Ramon B. Gustilo, 775
Nesbit, Mark E., Jr.: Ewing's Sarcoma. 513
New Approaches to the Treatment of Manic Depressive Illness. Edward A. Wolpert, 576
Niedringhaus, R. D., Aas, Johannes and Sanford, J. B.: Congenital Factor VII Deficiency. Safety of Surgery without Preoperative Transfusion. 791
Nivatvongs, Santhat and Goldberg, Stanley M.: Experience with Colonoscopic Polypectomy. Review of 700 Polyps. 197
Non-Hodgkin's Malignant Lymphoma. Clara Derber Bloomfield, 533
Nonsteroidal Anti-Inflammatory Drugs. Richard B. Tompkins, 677

N (continued)

Nutritional Management during Cancer Therapy. Athanasios Theologides, 547
Nutritional Management in Diabetes. Marion Franz, 41
Nuttall, Frank Q.: Obesity and Diabetes Mellitus. 19

O

Obesity and Diabetes Mellitus. Frank Q. Nuttall, 19
Ocular Changes in Diabetes. Howard D. Gilbert, 22
Olness, Karen: Cultural Aspects in Working with Lao Refugees. 871
1,000 Renal Transplants at the University of Minnesota 1963-1977. Bruce G. Sommer, David E. R. Sutherland, Carl M. Kjellstrand, Richard J. Howard, S. Michael Mauer, Richard L. Simmons and John S. Najarian, 861
Opportunistic Infections in Patients with Cancer. Bruce A. Peterson, 539
Osterholm, Michael and Andrews, John S., Jr.; Viral Hepatitis in Hospital Personnel in Minnesota. Report of a Statewide Survey. 683

P

Paisner, Hyman M.: Vertigo as a Hallucination or Illusion. 60
Parkinson's Disease, Huntington's Disease and Tardive Dyskinesia. Neurochemical Pathology and Treatment. Eduardo S. Tolosa, 101
Pediatric Cardiology at Children's Health Center First Five Years. Harold Katkov, 411
Peterson, Bruce A.: Acute Non-Lymphocytic Leukemia in Elderly Patients. 531
Peterson, Bruce A. and Briscoe, Kathleen: Investigational New Drugs in Cancer Chemotherapy. 536
Peterson, Bruce A.: Opportunistic Infections in Patients with Cancer. 539
Peterson, Charles R. and Helseth, H. K.: Survival after Coronary Artery Bypass Surgery. Significance of Preoperative Left-Ventricular Function. 813
Peterson, Hamlet A., Fitzgibbons, Timothy C. and Arata, Michael A.: Snowmobile Injuries in Children. 193
Peterson, Michael R. and Levy, Barry S.: Misconceptions about Possibly Rabid Animals that Have Bitten Humans. 266
Phenylbutazone-Induced Hepatitis. Thomas R. Mayer, 349
Physicians, Pharmacists and Refills. Lowell J. Anderson, 615
Planning A Treatment Program for the Patient with Rheumatoid Arthritis. John G. Mayne, 250
Post-Operative Headache. A Manageable Complication. John B. Brainard, 247
Potential Future Modes of Therapy in Diabetes Mellitus. John E. Gerich, 46
Prenatal Detection of Genetic Diseases. Richard P. Bendel, 135
Preschool Screening: Right or Ritual? John F. Hick, 373
Prevalence of Intestinal Parasites in a Laotian Immigrant Community. Neal R. Holtan, Kent B. Crossley, and Constance N. Pries, 749
Prewitt, Leland H., Jr. and Sane, Shashikant M.: Lateral Decubitus Radiograph of the Chest in Pediatric Radiology. An Additional Use. 423
Priest, James D.: Arthroscopy of the Knee. Another Diagnostic Technique. 710
Priest, James D.: Diagnosis of Acute Knee Injuries. 657
Proximal Tibial Metaphyseal Fractures in Children. A Complication. Richard J. Aadalen, 785
Psychopharmacology and Family Practice. Harley Racer, 91

PRESIDENT'S LETTER

Flom, Robert S.:
  Health Care Cost Commission's Report (February) 75
  Litigation Alligators (January) 5
  MMA is Constantly Working for Us (March) 145
  My Special Invitation to You (April) 217
  The Presidency (May) 313
Johnson, Frank E.:
  June-389
  July-477
  August-571
  September-629
  October-701
  November-771
  December-853

R

Racer, Harley: Psychopharmacology and Family Practice. 91
Recognition and Care of the High Risk Pregnant Patient and Neonate. Jack L. Strobel, 133
Reinertsen, James: Diagnosis of Rheumatoid Arthritis. 185
RH Isoimmunization Prevention Program in a Community Hospital. Arthur C. Aufderheide, 181
Rice, Carl O.: "We'll See You in A Moment". 188
Rockswold, Gaylan L. and Seljeskog, Edward L.: Traumatic Atlantocranial Dislocation with Survival. 151
Role of Gastrointestinal Endoscopy and Peritoneoscopy in the Diagnosis of Cancer. I Dodd Wilson, 494
Role of Nuclear Medicine in Oncology. Merle K. Loken and Mathis P. Frick, 491
Role of Physical Medicine and Rehabilitation in the Care of Rheumatoid Arthritic Patients. Mehrsheed Sinaki, 358
Role of Prospective Medicine in Health Care. Thomas A. Fenger, 841
RPAP — A Boon to Rural Minnesota. James K. Heid, 826

S

Salicylates. Richard B. Tompkins, 613
Schiele, Burtrum C.: Food and Drug Administration Regulation of Clinical Psychopharmacology. 593
Scintiangiographic Identification of Lesion Producing Foix-Alajouanine Syndrome. Clarence E. Henke, John M. Wolff, and Rex B. Shafer, 653
Septicemia and Pleural Effusion from Eikenella Corrodens. A Normal Mouth Inhabitant. Paul Stiegler, 789
Shilling, Bruce B., Wisiol, Erich S., Poley, Brooks J. and Purcell, Thomas' W.: Anterior Cranial Vault and Bony Orbit in Infancy. Craniofacial Surgery. 399
Shock Lung: An Overview. Michael A. Harris, 727
Sigel, Melvin E.: Dizziness. 59
Sinaki, Mehrsheed: Role of Physical Medicine and Rehabilitation in the Care of Rheumatoid Arthritic Patients. 358
Singher, Lawrence J.: Idiopathic Thrombocytopenic Purpura in Childhood. 455
Skiing Injuries to the Urinary Tract. T. A. Hildreth, A. S. Cass, and A. U. Khan, 155
Snowmobile Injuries in Children. Hamlet A. Peterson, Timothy C. Fitzgibbons, and Michael A. Arata, 193
Snyder, Bruce D.: An Efficient Approach to the Mental Status Examination. 901
Sommer, Bruce G., Sutherland, David E. R., Kjellstrand, Carl M., Howard, Richard J., Mauer, S. Michael, Simmons, Richard L. and Najarian, John S.: 1,000 Renal Transplants at the University of Minnesota 1963-1977. 861
Spencer, Bernard J.: Uncommon Inguinal and Scrotal Lesions in Infants. 435

S (continued)

"Square Knot" That Slips. John Strickler and Paul G. Gannon, 643
Steffes, Michael W. and Oppenheimer, Jack H.: The Laboratory Evaluation of Thyroid Function. 162
Stickel, Franklin R., Chisholm, Tague C. and Benson, David D.: Advances in Oral-Facial Deformity Reconstruction. 405
Stiegler, Paul: Septicemia and Pleural Effusion from Eikenella Corrodens. A Normal Mouth Inhabitant. 789
Strickler, John and Gannon, Paul G.: The "Square Knot" That Slips. 643
Strobel, Jack L.: Recognition and Care of the High Risk Pregnant Patient and Neonate. 133
Suggestions for Medical Screening of Southeast Asian Refugees. Andrew G. Dean, 753
Surgery's Reawakening. (1937-77). Owen H. Wangensteen, 879
Surgical Treatment of Uremic Pericarditis. David S. Hodge, Christina M. Comty, and Hovald K. Helseth, 323
Survival after Coronary Artery Bypass Surgery. Significance of Preoperative Left-Ventricular Function. Charles R. Peterson and H. K. Helseth, 813
Swazey, Judith P.: Chlorpromazine's Entrance into Psychiatry. An Extremely Interesting Product. 81
Syllabus. J. S. Welch, 59

SUPPLEMENTS

Minnesota Cervical Cancer Mortality Study 1971-72. Peter E. Fehr, Arthur H. Bearon and Konald A. Prem. March issue
New Directions for Health Care. Report and Recommendations of the Minnesota Medical Association's Commission on Health Care Costs 1979. May issue
Roster of the Minnesota Medical Association. September issue

T

Television and Children. A Physician's Guide. Robert Devney and Robert W. ten Bensel, 833
Testicular Surprises in Two Apparently Healthy Young Men. Miles J. Jones and Gene P. Siegal, 671
Theologides, Athanasios: Nutritional Management during Cancer Therapy. 547
Toledo-Pereyra, Luis H., Simmons, Richard L., Olson, Leslie C. and Najarian, John S.: Cadaver Kidney Transplantation. Effect of Hypotension and Donor Pretreatment with Methylprednisolone and Phenoxybenzamine. 159
Tolosa, Eduardo S.: Parkinson's Disease, Huntington's Disease and Tardive Dyskinesia. Neurochemical Pathology and Treatment. 101
Tompkins, Richard B.: Nonsteroidal Anti-Inflammatory Drugs. 677
Tompkins, Richard B.: Salicylates. 613
Tracheal Cylindroma. Report of a Case with External Tracheal Prosthesis. Richard C. Woellner and Alan C. Hymes, 660
Traumatic Atlantocranial Dislocation with Survival. Gaylan L. Rockswold and Edward L. Seljeskog, 151
Treatment of Ununited Fractures Adjacent to Joints. Frank C. Hui, Mark B. Coventry, George D. Veasy and Miguel E. Cabanela, 895
25 Years of Psychopharmacology. Special Issue — Part II. F. S. Abuzzahab, Sr. 574, Part I, 79

U

Uncommon Inguinal and Scrotal Lesions in Infants. Bernard J. Spencer, 435
Use of Imaging Techniques in Cancer Diagnosis. Samuel Feinberg, 489
Use of 1-desamino-8-D-arginine Vasopressin (DDAVP) in the Management of Neurogenic Diabetes Insipidus. (Multiple Etiologies in Pediatric Patients). David R. Brown and Donald L. Uden, 427

V

Van Tassel, Robert: The Cardiovascular System and Dizziness. 63
Variant A-V Block Secondary to Concealed Conduction. Kyuhyun Wang and David A. Berman, 713
Venters, H. D.: Juvenile Rheumatoid Arthritis. 463
Vertigo as a Hallucination or Illusion. Hyman M. Paisner, 60
Vertigo, A. B. Baker, 60
Viral Hepatitis in Hospital Personnel in Minnesota. Report of a Statewide Survey, Michael Osterholm and John S. Andrews, Jr., 683
Vosika, Gerald J.: Adjuvant Therapy of Malignant Melanoma. 515
Vosika, Gerald: Immunotherapy in Cancer. Current Status and Future Prospects. 549
Vosika, Gerald: Lung Cancer. Current Evaluation and Therapy. 519

W

Walsh, William E.: Atopic Dermatitis Associated with Citric and Malic Acid Intolerance. 637
Wang, Kyuhyun and Berman, David A.: Variant A-V Block Secondary to Concealed Conduction. 713
Wangensteen, Owen H.: Surgery's Reawakening (1937-77) 879
Weigent, C.E. and Hanson, K.C.: Micropolycystic Liver Occurring in an Adult with Gluten Enteropathy. 231
Weiner, Michael J.: Cholelithiasis in a Child without Hemolytic Anemia. 223
Welch, J. S.: Farewell Old QACME. 137
Welch, J. S.: Syllabus. 59
"We'll See You in A Moment" Carl O. Rice, 188
Wilson, I. Dodd: Role of Gastrointestinal Endoscopy and Peritoneoscopy in the Diagnosis of Cancer. 494
Woellner, Richard C. and Hymes, Alan C.: Tracheal Cylindroma. Report of a Case with External Tracheal Prosthesis. 660
Wolpert, Edward A.: New Approaches to the Treatment of Manic Depressive Illness. 576

Y

YaDeau, Richard, Bates, Henry A. and Fortuny, Ignacio: Lung Cancer Patients Treated with Corynebacterium Parvum. Phase I Toxicity Study. 673

Z

Zuelke, David L.: American Diabetes Association. 55

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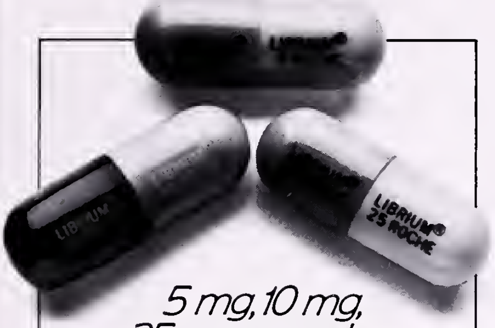

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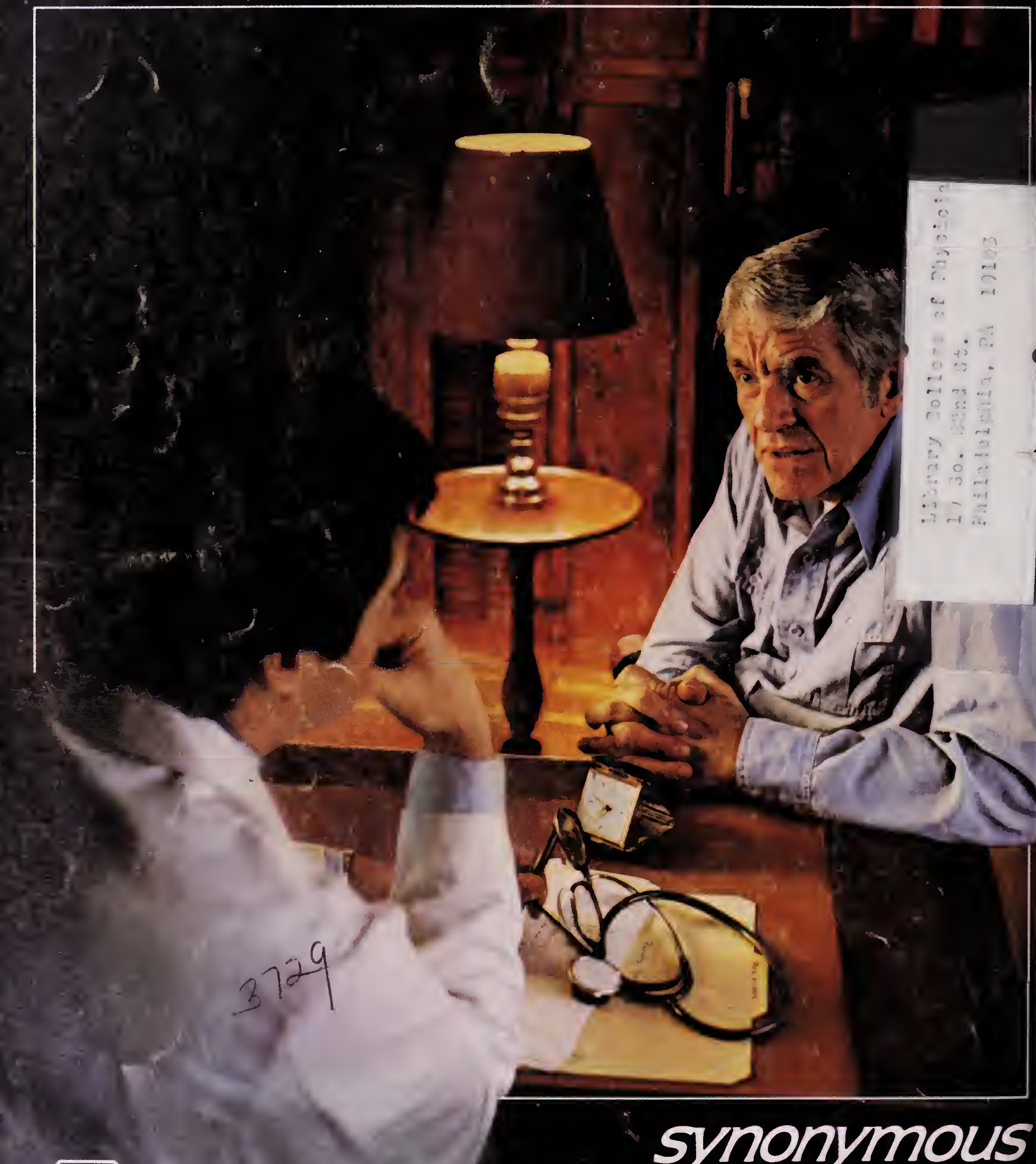

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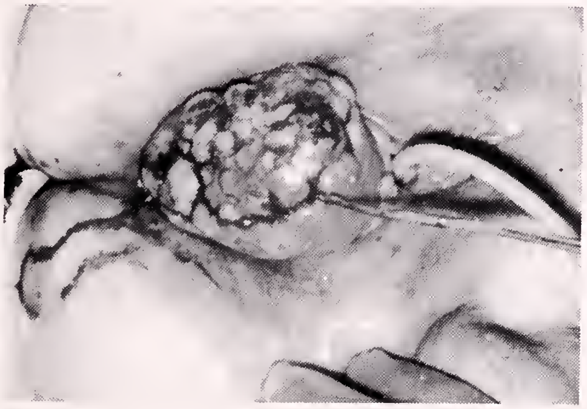

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Minnesota Cervical Cancer Mortality Study 1971-72

PETER E. FEHR, M.D.,* ARTHUR H. BEARON, M.D.* and KONALD A. PREM, M.D.*

A retrospective study of all (140) cervical cancer deaths in the State of Minnesota in 1971-72 was undertaken. Each of these cases was studied under the following categories: (1) Adequacy of care in the five-year period prior to the onset of symptoms. (2) The adequacy of care from the onset of symptoms to the tissue diagnosis. (3) The pre-treatment evaluation. (4) The treatment. (5) The post-treatment follow-up. (6) Secondary treatment, if any. (7) Follow-up of any secondary treatment. (8) Palliative treatment. (9) To determine responsibility for death. (10) To consider the correctness and adequancy of the death certificate.

This report deals with the findings of the study and gives suggestions for the improvement of the cervical cancer mortality rate.

IN PAST DECADES the outlook for patients with cervical cancer has substantially improved. Two-thirds or more of all patients with squamous cell carcinomas of the cervix now have the disease diagnosed before it becomes invasive, at a time when the proportion that can be cured with proper treatment approaches 100%.

The absolute number of invasive cancers of the cervix in the United States appears to have remained relatively stable for the past 20 years, but effective screening has been responsible for the decline in morbidity and mortality. For example, in Louisville, Kentucky, between 1956 and 1958 when more than 90% of women were screened by Pap smear, the incidence of invasive squamous cell carcinoma of the cervix in patients aged less than 50 decreased by 43.2%. The number of Stage I cancers increased 78%, meaning that a larger percentage of patients with invasive lesions came to therapy at a stage where the cure rates are higher.[1] In the remainder of Kentucky where there were no mass screening programs during this same period, the death rate from cervical cancer remained the same.[2] Similar improvement presumably due to mass screening programs has been reported in British Columbia[3] and New York[4] where death rates have decreased by more than 50%.

The distribution of cervical cancers by stage of the disease at diagnosis has changed little in the past 20 years. Only about 50% of patients have disease classified as ``localized'' at the time of diagnosis. The 10-year survival rate for patients with clinical cancers of the cervix is reported to be slightly higher than 50%.

This retrospective cancer mortality study was undertaken by a special subcommittee under the auspices of the Obstetrics, Gynecology and Maternal Health Committee of the Minnesota Medical Association with the approval and endorsement of the Minnesota Obstetrical and Gynecological Society, the Minnesota Society of Clinical Pathologists, and the Cancer Committee and Board of Trustees of the Minnesota Medical Association. It was funded by the Northlands Regional Medical Program, the Minnesota Division of the American Cancer Society, and the Minnesota State Department of Health.

In Minnesota in recent years the number of cancer deaths due to cervical neoplasia has declined steadily, from 101 deaths in 1960 to 91 in 1965, and 75 in 1967. However, although improved diagnosis and treatment can now locate and cure most cervical cancer, women continue to die from it. A project was developed to study fatal cases of cervical cancer in Minnesota in the hope that identifying defects in methods of diagnosis, treatment, and follow-up may lead to still greater decline in death rates. Data was used from death certificates to study all cases of women who died of cervical cancer between January 1, 1971 and December 31, 1972.

Our objective was to establish a cancer mortality study analogous to the well-known Minnesota Maternal Mortality Study. The results are hoped to be useful to the medical profession in its programs for continuing medical education and that they will benefit the women of Minnesota. By elucidating errors both of commission and of omission, we hope to stimulate preparation of postgraduate study programs for physicians and education of the lay public in the early diagnosis of

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Study Supported by: Northlands Regional Medical Program, Project P-45, Minnesota State Board of Health and Minnesota Division of the American Cancer Society.

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Procedure

The Cervical Cancer Mortality Committee, composed of two gynecologic oncologists, three practicing gynecologists, three family practitioners, three pathologists, one radiotherapist, one biostatistician, one State Board of Health representative, one Maternal Health Committee representative, and three investigators, formulated a suitable protocol and reviewed all collected data. Because no previous investigation of this type has been reported, criteria similar to those used by the Maternal Mortality Study Committee were established.

Detailed investigations began with the decedent's health in the five years prior to the diagnosis of malignancy. The following categories were set up for evaluation.

1. Adequacy of care in the five-year period prior to the onset of symptoms
2. Adequacy of care from the onset of symptoms to the tissue diagnosis
3. Pretreatment evaluation
4. Treatment
5. Posttreatment follow-up
6. Secondary treatment, if any
7. Follow-up of any secondary treatment
8. Palliative treatment
9. Responsibility for death
10. Correctness and adequacy of death certificate

Materials and Methods

All death certificates listing carcinoma of the cervix or uterus as the cause of death for the calendar years 1971 and 1972 were extracted by the Minnesota State Health Department and sent to the investigative members of the committee. The certificates listing cancer of the uterus as the cause of death were reviewed to determine whether the primary site of cancer was the corpus or cervix. If a decison could not be made as to the origin of the disease, a letter was sent to the certifying physician who in many instances was able to determine the source of the primary disease from records. When the certifying physician could not, collected data were presented to the committee for a decision. Most death certificates were complete and accurate.

Cases excluded from the study were those in which primary treatment had been given outside the state of Minnesota, except for the contiguous areas on the borders.

To initiate a case study, the investigators mailed a questionnaire to the physician who signed the death certificate requesting the names of all physicians involved in the total care of the patient as well as dates, places, and details of all hospitalizations. When each questionnaire was returned, investigators attempted to locate all cytologic smears taken from the patient during the five years prior to the diagnosis of malignancy, as well as all histologic material associated with the case. If autopsy slides were available, and applicable, these were requested. All cytologic and pathologic material was independently reviewed by the three pathologists on the committee to confirm the original diagnoses. All physicians who participated in the patient's care were asked for detailed descriptions of the care, including therapy.

In each case the pool of data was put in rough chronologic form. In most cases the investigators personally reviewed hospital and office records and interviewed one or more of the participating physicians to obtain as accurate an account as possible of the patient's history, diagnosis, treatment, and follow-up care. All Pap smear, Xray, and pathology reports; operative notes; consultations; and radiation therapy summaries were copied for committee examination.

TABLE 1

Diagnosis of Cervical Malignancy in 140 Patients in Relation to the Menopause

	Patients				
	Premenopausal		Postmenopausal		
FIGO Stage	Squamous	Adenocarcinoma	Squamous	Adenocarcinoma	Total
IA	1		4		5
IB	8	2	11	4	25
IIA	9		10	2	21
IIB	12		21	6	39
IIIA	1		6	1	8
IIIB	6		15		21
IV	2	1	10		13
Unstaged	—	—	7	1	8
Total	39	3	84	14	140

The records were reviewed and interviews conducted by physician investigators knowledgeable and experienced in the detection, diagnosis, and treatment of gynecologic malignant disease.

After collection of all data, a chronologic summary of each case was prepared and submitted to the committee for final review and evaluation. The committee evaluated each case according to the previously listed 10 major categories and judged the care in each category to have been adequate or inadequate.

Results

Criteria for inclusion in the study were satisfied by 140 cases. The distribution of the cases by FIGO stage, histologic type, and relation to menopause is tabulated in Table 1. In cases where staging was not done but the description of the neoplasm was adequate, the investigators retrospectively assigned a FIGO stage. Those listed as unstaged were not adequately described to permit even tentative staging. Seventy percent of the cases were in postmenopausal women, and almost 88% were squamous cell carcinoma.

Five of the postmenopausal patients had squamous cell carcinomas of a cervical stump not removed at previous subtotal hysterectomy. One of these was a Stage IB, one Stage IIA, and three were Stage IIB.

Care before Onset of Symptoms

Gynecologic care in the five years prior to the onset of symptoms was considered adequate if a pelvic examination and a Pap smear were performed annually, as recommended by the American Cancer Society and the American College of Obstetricians and Gynecologists. If the five-year period in question antedated the widespread use of cytologic screening in Minnesota, this standard of adequate care was liberalized. Only 20, or 14% of the patients had received adequate care according to the criteria established, slightly more premenopausal than postmenopausal patients. The committee determined that in 111 of the remaining 120 cases, or 93%, inadequate care may have contributed to the death of the patient.

Assignment of responsibility for inadequate care is shown in Table 2. The committee held the patient responsible alone or in conjunction with her physician, in 70% of all cases; among premenopausal patients, 79% of the responsibility was charged to the patient alone. The major care problem was failure to have regular annual pelvic examinations and Pap smears. The physician alone was responsible for inadequate care in 26% of cases. The most common error was failure to do a pelvic examination and Pap smear regularly on patients being treated for other medical or surgical conditions. Review of hospital records confirmed that in 46% of admissions for nonrelated conditions, the pelvic exam was deferred. Deferring an examination implies that it will be done later, but there is rarely any evidence that it was.

In a review of all hospitalizations of the 140 patients in the five years prior to the diagnosis of cervical malignancy it was found that four patients had had a hemorrhoidectomy, three had cataract surgery, and four had a possible cerebrovascular accident. In all cases the pelvic exam was "deferred" at the time of admission, yet not one of these patients was examined subsequently until symptoms of cervical cancer appeared. Two of four patients hospitalized for nonrelated conditions within two months of the diagnosis of invasive cervical malignancy were listed on the admission History and Physical as having pelvic examinations "deferred". The other two patients were listed on the chart as having a "negative pelvic", only to have Stage IIB disease confirmed within one month.

Adequacy of care from the onset of symptoms to the establishment of the diagnosis is related to the menopause in Table 3. The committee assessment of responsibility for inadequate care prior to the onset of

TABLE 2

Responsibility for Inadequate Medical Care in Five Years Prior to Symptoms as Related to the Menopause

	Total		Pre-Menopausal		Post-Menopausal	
Patient	71		26		45	
Refused exam		7		3		4
No physician visits		64		23		41
Physician	31		3		28	
Pelvic and Pap smear not done		25		0		25
Pap smear not done		1		1		0
Inadequate exam		3		1		2
Lesion misinterpreted		2		1		1
Patient & Physician	13		4		9	
Nursing Home	5				5	
Total	120		33		87	

symptoms related to menopause is found on Table 4. Adequacy of care both before and after the onset of symptoms was analyzed according to the specialty of the primary care physicians as shown in Table 5. Family physicians cared for 79% of the patients and gynecologists for 11%. Of all primary care physicians, 31% did not perform regular adequate pelvic exams and Pap smears on their patients. However, in the committee's judgment only 12% provided inadequate care after the onset of symptoms.

Because both physicians and patients were disease-oriented, the adequacy of care improves after the onset of symptoms. Still, although 80 patients (57%) received adequate care after the onset of symptoms, 60 (43%) received inadequate care even then, and the committee ruled that the inadequate care contributed to the death of 50 of them. Although more than 70% of the premenopausal patients received inadequate care both before and after onset of symptoms, only 37% of the postmenopausal patients received inadequate care after onset of symptoms.

The patient was judged responsible for inadequate care in 40 cases (67%) because she failed to seek medical help for symptoms. Adequate care from onset of symptoms was defined on the patient's part, as reporting unusual symptoms, i.e., abnormal vaginal bleeding, and on the physician's, prompt pelvic examinations with suitable diagnostic steps being taken to seek the cause for the symptoms. Some patients refused pelvic examinations while at a physician's office for other reasons, and some didn't bother to report their symptoms.

Diagnosis

The most common physician error was failure to interpret a cervical lesion as possibly malignant. A Pap

TABLE 3

Adequacy of Medical Care from Onset of Symptoms to Diagnosis as Related to the Menopause

Care	Total		Pre-Menopause		Post-Menopause	
Adequate	80					
Inadequate	60		24		36	
Contributory		50		19		31
Non-contributory		10		5		5
Total	140		24		36	

TABLE 4

Responsibility for Inadequate Care from Onset of Symptoms to Diagnosis as related to the Menopause

Care	Total		Pre-Menopause		Post-Menopause	
Patient	40		17		23	
No physician visits		30		15		15
Refused exam		8		2		6
Didn't report symptoms		2		0		2
Physician	17		7		10	
Lesion misinterpreted		13		7		6
Pelvic not done		4		0		4
Patient & Physician	2				2	
Nursing Home	1				1	
Total	60		24		36	

TABLE 5

Adequacy of Care before and after Onset of Symptoms as Related to Specialty of the Primary Physician

Specialty	No.	%	Inadequate Care Before Onset	Inadequate Care After Onset
Family Practice	110	79	38	14
Gynecology	15	11	0	1
Internal Medicine	10	7	4	1
General Surgery	4	3	2	1
Osteopathy	1	<1	0	0
Total	140		44	17

smear reported as Class I, II, or even "unsatisfactory" was considered sufficient evidence for the physician to consider a cervical lesion as benign. However, the committee held that care was adequate only if unusual cervical lesions were biopsied in spite of a negative Pap smear. A cervical biopsy can be done in the office with a minimum of pain, inconvenience, and expense to the patient, and earlier diagnoses of cervical malignancy would have been made had this procedure been carried out. The committee recommends that every physician who does pelvic exams either have a punch biopsy forceps in the office or refer patients needing a biopsy to someone who does.

Diagnostic procedures used to determine whether or not a cervical lesion was malignant were designated by the committee as appropriate or inappropriate as shown in Table 6. The committee held that the appropriate diagnostic procedure was a cervical biopsy when a cervical lesion was visible and a conization when no lesion was visible. Diagnostic procedures were judged appropriate in cases of cervical adenocarcinoma only if a fractional dilatation and curettage (D & C) had been performed to rule out endometrial primary disease.

The diagnostic procedures were judged by the committee to be appropriate in 79% of the cases. Cervical biopsy, deemed the only appropriate diagnostic procedure in a premenopausal patient with a visible cervical lesion was done in 59% of the patients. In five cases, however, the biopsy was considered inadequate or inappropriate. Two were excessively large approaching the size of a cone biopsy and requiring massive blood transfusions. One biopsy was too small and the true diagnosis was missed, resulting in an inappropriate hysterectomy. In two postmenopausal patients the cervical biopsy showed adenocarcinoma of the cervix. The committee ruled that these two patients should have had a fractional D & C performed to rule out endometrial primary disease with cervical extension. Because this was not done, the disease was considered to be of cervical origin in both cases.

A D&C and cervical biopsy was carried out in 22% of the patients, but in 11 it was considered inappropriate. In all of these cases the patient had a visible cervical lesion, and since there was no need to consider the possibility of primary endometrial disease, a cervical biopsy alone would have been adequate for diagnosis. The D & Cs were judged unnecessary and therefore inappropriate. D & C without cervical biopsy was the procedure in nine patients, none of whom had visible cervical lesions. One D & C was considered inadequate because the tissue in the cervix was not adequately sampled; a hysterectomy specimen from this patient subsequently showed a primary endocervical malignancy.

Conization of the cervix with D & C was done in six cases, four of which were ruled inappropriate. In all of these cases the patient had a visible cervical lesion, yet a conization was done that resulted in unnecessary hemorrhage. Of five conizations without D & C, three were deemed inappropriate because these patients also had visible cervical lesions. Many of the conization procedures were done because the pathologist suggested it on the report of a suspicious Pap smear. Either the patient was referred to a general surgeon or the family practitioner carried out a conization of the cervix, in the presence of a visible lesion.

In six cases the diagnosis was made by hysterectomy, with no attempt at preoperative evaluation, and in all of these cases significant clinical disease would have warranted either biopsy or D & C before hysterectomy. In two additional cases, both mentioned earlier, the preoperative diagnostic procedures performed were inadequate, and the diagnosis of cervical carcinoma ultimately was made by hysterectomy: In

TABLE 6

Procedures used to establish Diagnosis of Cervical Carcinoma

	No.	%	Inadequate or Inappropriate #	Inadequate or Inappropriate %
Appropriate	111	79		
Inappropriate	29	21		
Cervical biopsy	83	59	5	6
D & C with cervical biopsy	29	22	11	38
D & C without cervical biopsy	9	6	1	11
Cone biopsy with D & C	6	4	4	66
Cone biopsy alone	5	4	3	60
Hysterectomy	6	4	6	100
Pap smear only	1		1	100
No histologic diagnosis (clinical diagnosis only)	1		1	100
Total	140		32	21

one the cervical biopsy was too small, and in the other D & C was done without a cervical biopsy.

In one case only a Pap smear was done because the physician decided no further workup was warranted. In another case only a clinical diagnosis was made because the patient refused the necessary diagnostic procedures.

One patient had several diagnostic procedures performed after vaginal and cervical biopsies established a diagnosis of squamous cell carcinoma of the cervix, stage IIIA. These procedures included a cervical conization, laparoscopy, and lysis of intra-abdominal adhesions. The committee ruled that these procedures were totally inappropriate and unnecessary for therapeutic management.

Gynecologists and family physicians most often selected the appropriate diagnostic procedure. The committee judged diagnostic techniques inappropriate in 29% of cases overall; in 14% of gynecologist's patients, 22% of family practitioner's patients, and 47% of general surgeon's patients.

The specific inappropriate diagnostic procedure is correlated with the specialty of the physician in Table 7. The most inappropriate procedure, simple hysterectomy in the face of invasive carcinoma, was performed in eight cases. It is probably the only inappropriate procedure that directly affected the patient's prognosis.

There were 10 errors in interpretation of pathologic and cytologic preparations: nine in Pap smears and one in biopsy tissue. False-negative and other inaccurate interpretations of Pap smears have been considered a problem in screening for cervical malignancy. The reported incidence of false-negative Pap smears in squamous cell carcinoma of the cervix is between 10 and 25%. In this study some Pap smears were found to have been misinterpreted. One diagnostic laboratory, using a fluoroscent staining technique, failed to identify tumor cells in one patient's Pap smears, with the result that diagnosis was delayed for three years until obvious clinical malignancy developed. The patient died soon after therapy.

A frustrating problem uncovered by the investigators in this study is that many cytology laboratories discard Class I Pap smears after 6 to 18 months. This, of course, prevents a review of the original interpretation. Nine Pap smears that had been reported as Class II originally were interpreted as Class IV or V by the committee pathologists on blind reevaluation.

Another problem found by the committee was the failure of the clinician to repeat the Pap smear when the report was "unsatisfactory". This error accounted for three late tumor detections.

The histopathologic diagnosis was correct in all but one of the 389 sets of slides (876 slides in all). The

TABLE 7

Inappropriate Procedures Related to Specialty of Physician

	Physician FP	OBG	Surg	Total
D & C	5	6	1	12
Hysterectomy	3	1	4	8
Cone biopsy	1	—	2	3
D & C, cone biopsy	2	1	—	3
Excessive size of biopsy	2	—	—	2
Multiple procedures	—	1	—	1
Total	13	9	7	29

TABLE 8

Pretreatment Consultation

	No.		%	Inadequate No.	%
Indicated	125		89		
Appropriate		107	86		
Specialty of Consultant					
Gynecologist	58		47	8	13
Gynecologist & Radiotherapist	35		30	5	13
Radiotherapist	12		10	4	33
General Radiologist	7		7	7	100
General Surgeon	6		6	5	83
Inappropriate		11	9		
Patient refused		4	3		
None		3	2		
Not indicated*	15		11		

*Primary physician was a gynecologist

single tissue error resulted in a simple hysterectomy that transected an invasive carcinoma.

As important as an error in slide interpretation was the clinician's failure to read the tissue report. A simple hysterectomy was performed on one patient because her physician failed to recognize a stage IIB squamous cell carcinoma of the cervix, although a pathology report on material from a D & C performed on her 18 months earlier for abnormal bleeding stated "abnormal squamous epithelium — suggest cervical biopsy." This report was unknown to the clinician until the case investigator pointed it out on review of the patient's hospital record.

Consultation

The committee considered pretreatment consultation appropriate only if done by a gynecologist or a radiation therapy consultant trained in the management of gynecologic cancer. The adequacy of pretreatment consultation and the specialty of the consultants are analyzed in Table 8. Of the 117 appropriate consultations, 85 were regarded as adquate.

The ACOG Technical Bulletin No. 24 of August, 1973 recommends that pretreatment evaluation for cervical cancer consists of:

1. A good general medical evaluation with complete blood count, urinalysis and culture, blood urea nitrogen (BUN), creatinine, and two-hour postprandial blood sugar determinations, and an electrocardiogram (EKG).
2. Studies to determine the extent of the disease process — chest Xray, intravenous pyelogram (IVP), cystoscopy, proctoscopy, and barium enema.
3. Clinical staging of the lesion.

The committee, however decided that for purposes of this study a minimum evaluation would consist of a chest Xray, clinical staging of the lesion, an IVP, and cystoscopy.

The pretreatment evaluation of the 140 cases is tabulated in Table 9. Only 68% of patients received an accurate pretreatment clinical staging, only 54% an IVP, and only 49% a cystoscopic examination. In general, the premenopausal patients received more thorough evaluation than the postmenopausal patients. A pretreatment evaluation of the urinary tract, IVP and cystoscopy, was done in 62 patients. Of the 54 patients without adequate pretreatment evaluation, 34 were managed by appropriate consultants. Responsibility for the management of patients who had inadequate pretreatment evaluation is tabulated in Table 10.

Therapy

The primary treatment of the cervical malignancy varied widely in type but the committee judged

TABLE 9

Pretreatment Evaluation

			Premenopausal		Postmenopausal	
	No.	%	No.	%	No.	%
International Staging						
Accurate	95	68	29	70	66	67
Inaccurate	5	3	1	1	4	5
Not done	40	29	12	29	28	28
Total	140	100	42	100	98	100
IVP	75	54	28	67	47	48
Cystoscopy	69	49	27	64	42	43
Proctoscopy	56	44	23	55	33	34

TABLE 10

Specialty of Consultant Responsible for the Patients without Minimum Pretreatment Evaluation

	No.	%
Gynecologist	20	37
Radiotherapist	9	17
Gynecologist primary physician	5	9
Gynecologist & radiotherapist	5	9
General surgeon	4	7
General radiologist	4	7
General radiologist & surgeon	1	2
No consultation — patient's decision	4	7
No consultation — physician's decision	2	5
Total	54	100

primary therapy appropriate for 80% of patients. Only 10% of patients were ruled to have had inappropriate therapy. Palliative therapy only was given to 3% and no therapy to 14 patients (10%). Of these, four refused therapy, three died before therapy was begun, and three had such advanced disease that therapy was deemed valueless by the responsible physician.

Primary therapy is tabulated in Table 11. In all eight cases of patients treated by hysterectomy without a preoperative diagnosis of malignancy, the disease was stage IB to stage IIIB by clinical description.

After the inadequate primary surgical therapy was given to 10 patients, postoperative radiation therapy was given immediately to only four. Three patients never received radiation therapy, and three received it only after proved recurrence. One of the latter received an adequate dose of external beam in combination with radium, while the other received an inadequate dose of radium following an adequate dose of external beam therapy. All other radiation therapy was delivered from external sources only. Because adequate radiation may salvage some patients, the committee recommends immediate postoperative therapy with both external beam and radium implants when surgical treatment is inadequate. In general, the study experience indicated that when inappropriate surgery was followed by radiation therapy, that therapy was either too little or too late, or both.

In the 19 cases in which primary surgical therapy was given, the operating surgeon was a gynecologist in nine, a general surgeon in seven, and a family physician in three. Whereas only one of the gynecologists was judged to have given inadequate or inappropriate care, the committee believed all the others had done so, for an overall rate of inadequate and inappropriate surgical therapy of 58%.

The type of primary irradiation therapy provided in the treatment of 107 patients is shown in Table 12. The

TABLE 11

Primary Therapy

	No.	%	Inadequate or Inappropriate #	%
Irradiation	107	76	24	22
Surgery	16	12	10	62
Adequately planned primary surgery	8	42		
Adequate preop irradiation	(2)			
No preop irradiation	(6)			
Hysterectomy without previous diagnosis of malignancy			8	42
Inadequately planned primary surgery			2	11
Inadequate preop irradiation and inadequate surgery			1	5
None	14	10		
Total	140		34	

TABLE 12

Primary Radiation Therapy

	No.	%	Inadequate or Inappropriate No.	%	Palliative No.	%
Adequacy and type:						
Cobalt-radium	80	75	11	14		
Cobalt only	12	11	7	58	5	42
Deep x-ray-radium	11	10	2	18		
Deep x-ray alone	2	2	2	100		
Radium alone	2	2	2	100		
Total	107	100	24	22		
Specialty of ordering physician						
Gynecologist & radiotherapist	41	40	7	17		
Gynecologist & general radiologist	35	32	3	8		
Radiotherapist	23	21	10	43		
General radiologist	8	7	4	50		
Total	107	100	24	22		

committee ruled that appropriate primary radiation therapy consisted of external beam combined with intracavitary and vaginal radium, producing approximately 8000 rads to point A and 5000 rads to point B.

Of the 11 patients considered to have been inadequately treated with cobalt and radium, the inadequate therapy was the result of patient problems in six: one patient refused a second radium application; in one case the radium slipped downward into the vagina, and the exact doses to points A and B were in doubt; and the general condition of four patients was too poor to allow completion of radium therapy.

The physician was judged at fault in five cases, in three of which the patient received inadequate radium dosage. In one of these three the gynecologist had miscalculated the radium dosage, and in the other two the radiotherapist decided the cervix was too small to allow the insertion of an intracervical tandem of radium without consultation with a gynecologist. Another patient had suboptimal radium distribution because of inappropriate application of the radium by the radiotherapist. In the fifth case there was a three-month time lag between the cobalt and radium therapy. No allowance was made for tissue recovery.

Cobalt therapy alone was used in 12 cases. In five it was considered to be palliative and in seven it was considered therapeutic but judged by the committee to be inadequate. Of these seven cases, the problem was attributable to the patient in four: one patient failed to continue therapy and was lost until her recurrence was found; two patients died while receiving cobalt therapy; and the tumor response was poor in the fourth and her condition too poor to continue therapy. In three cases the radiotherapist was judged to be at fault: One patient had been considered too old for radium therapy, despite this she lived two years after diagnosis and died of persistent disease, and in two cases the therapist, without gynecologic consultation, decided that the cervix was too small for intracervical application of radium, and these patients also died of persistent disease.

Deep Xray and radium were used in the treatment of 11 patients and were considered inadequate in two; one because of suboptimal dosage of Xray and the other because of inadequate radium distribution. Both of these cases were considered by the committee to be the fault of the general radiologist who cared for the patients.

Two patients were treated by deep Xray alone. Radium was not given to one because her general condition was too poor. The second case was very unfortunate, however; the patient was young and healthy, but radium simply was not planned for her. She received a second course of cobalt several years later, again without radium, and finally died of persistent disease. The general radiologist who provided the initial deep Xray (250 KV) therapy was faulted, but the family practitioner who actually made the decision regarding therapy also should have been faulted.

Radium alone was used in two patients. The radium dosage in one was inadequate and in the other was determined to be inappropriate. In both of these cases the poor therapy was the fault of the general radiologist treating them.

Many of these errors in treatment could have been avoided by a team approach, with better communication between the individuals providing the external beam therapy and the radium therapy. ACOG Technical Bulletin No. 24 recommends that one

TABLE 13

Follow-up Care

	No.	%	No.	%
Adequate				
Gynecologist	35	59		
Family physician	20	34		
Internist	2	3		
General surgeon	2	3		
Total	59			
Inadequate care				
Patient	14	26		
Patient and physician	5	10		
Physician	34	64		
Gynecologist			14	
Family physician			10	
General surgeon			8	
Radiotherapist			3	
Internist			1	
General radiologist			1	
Total	53			

physician assume the responsibility to see that full therapy is completed. This study demonstrates the validity of that recommendation, and Table 12, in which the quality of radiation therapy is related to the specialty of the physician administering it, suggests that appropriate and adequate therapy is more often received when a gynecologist is part of the team.

Follow-up

The committee ruled that minimum criteria for adequate follow-up care included a pelvic examination and Pap smear every three months for the first three years after therapy and annually thereafter. Inadequate follow-up resulted in the late detection of persistent or recurrent disease, and late detection reduces the chance of successful secondary treatment.

In the 112 patients who received follow-up care, it was considered adequate in 59 (42%) and inadequate in 53 (39%). In 48 (91%) of the 53, inadequate follow-up care may have contributed to their deaths. The 28 patients who did not receive any follow-up care include two who discontinued treatments and did not return for follow-up, one who died immediately after primary treatment, two had had no treatment at all, and 23 who died within a short time after primary therapy. The adequate follow-up care was given primarily by treating gynecologists and family physicians.

Table 13 is an analysis of follow-up care according to the physician who gave it. Every patient treated for cervical cancer should be given follow-up care on a regular basis by a physician familiar with the early signs, symptoms, and physical findings of persistent and recurrent disease. In addition to a regular pelvic exam and Pap smear, an annual chest Xray and hemogram should be part of the follow-up. Any sign that suggests persistent or recurrent disease should be adequately evaluated immediately and the patient referred to a center where radical curative surgery or irradiation can be carried out, if appropriate.

Inadequate follow-up care was judged to be the patient's responsibility in 14 cases, or 26%. Of these 14 patients, 12 failed to return for examinations and two bluntly refused follow-up care altogether. In five cases, physician and patient were equally responsible — no organized plan was proposed for follow-up care, and the patient failed to return as requested. The physician was responsible for inadequacy of care in 64% of cases, either because there was no plan for follow-up or because the plan made was inadequate. In some cases the physician failed to recognize signs of advancing disease, which resulted in a delay in the diagnosis of persistent or recurrent disease.

The treatment of persistent and recurrent disease is tabulated in Table 14. Some kind of palliative therapy was carried out in 61 patients. Chemotherapy was administered as secondary and tertiary therapy in an attempt to arrest tumor growth when the patient was not a candidate for surgery or irradiation. None of this therapy was successful. Cobalt treatment was used in 25 patients, with limited success, and radium alone in three. Appropriate surgery was performed in one case and inappropriate surgery in two cases. The committee judged as inappropriate a radical hysterectomy in the presence of iliac vein obstruction by tumor. Four patients were treated with surgery designed to be curative. Of 28 patients refusing secondary therapy, 23 were older, postmenopausal patients.

The committee assigned responsibility for non-cure as follows: In 87 cases the patient was assessed with total or partial responsibility along with the physician (62%); the physician was judged wholly or partially responsible in 67 cases (48%); in four cases (3%) the nursing home in which the elderly patient resided ignored signs and symptoms and therefore was assessed the responsibility for non-cure. Twenty cases were considered not preventable (14%).

The primary physician was considered responsible for non-cure in 49 cases (45%). Autopsies were performed in 43 of the 140 cases.

TABLE 14

Treatment of Recurrent or Persistent Disease

	No.	%	No.
Palliative	61	65	
Chemotherapy (secondary)			29
Chemotherapy (tertiary)			6
Cobalt			25
Radium only			3
Appropriate surgery			1
Inappropriate surgery			2
Cobalt and radium			1
Refused	28	31	
Curative surgery	4	4	
Total	93		61

Discussion

For many years the problem of cervical malignancy has been discussed in terms of how to initiate educational programs to promote earlier detection and better long-term results. The American Cancer Society conducts a fine program of patient education, but additional educational effort is necessary to eliminate some last barriers of patient resistance. This study shows that the first priority is to make patients aware of the condition and what they can do about it. In a high percentage of cases, the patients had failed to seek a physician's advice, to request pelvic examinations and Pap smears, and to report early symptoms of malignancy — intermenstrual, postcoital, or postmenopausal bleeding.

A large number of premenopausal patients gave as their reason for not seeing a physician that they were not pregnant. Many women of reproductive age evidently believe that pregnancy is the only reason for them to see a physician.

Many patients in this study who did visit a doctor for nongynecologic medical problems received only spot checks. Their doctors neither gave them a pelvic examination and Pap smear nor asked the date of their most recent physical examination. Some physicians interviewed did not believe an annual physical and Pap smear were justified for their patients.

Some physicians are unable to recognize an abnormal cervix. The success of the Pap smear as a screening method has encouraged physicians to rely on it absolutely, even when a patient's cervix appears abnormal. Most physicians are not aware that Pap smears processed in commercial laboratories on a mass scale have a false-negative rate of 10 to 25%. For this reason a patient with an abnormal-appearing cervix should have either quadrant biopsies or biopsies directed by Schiller stain, or she should be referred for a directed biopsy under colposcopy. If routine Pap smears had been taken and biopsies made of abnormal cervices, many patients in this study might have been cured because therapy would have been undertaken at an earlier stage of the disease. Physicians who are not accustomed to managing problems that could be the result of malignancy should refer any patient with an abnormal appearing cervix to a gynecologist or gynecologic oncologist.

Several patients had a hysterectomy without proper preoperative diagnostic procedures to rule out carcinoma of the cervix. A cervical cancer may be present in a symptomatic patient and if a fractional curettage is not done prior to hysterectomy the cancer may be inadequately treated.

One patient in this series had a D & C performed, but the physician did not curette the endocervical canal separately from the endometrium. Because all curettings were submitted as endometrial curettings, the pathologist made the diagnosis of adenoacanthoma of the endometrium. The patient therefore was treated with a simple hysterectomy. The hysterectomy specimen showed an invasive squamous cell carcinoma of the cervix. This inappropriate therapy could have been avoided by fractional curettage with the endocervical and endometrial tissue fractions submitted separately.

Another fatal delay occurred because a physician was not aware of the pathologist's findings. A report of abnormal squamous epithelium in the curettage specimen was filed in the hospital record, but the pathologist's suggestion that the patient's cervix should be examined thoroughly and biopsied as appropriate to determine the source was not seen, because a copy was not sent to the physician's office. A year later, when total abdominal hysterectomy was performed for what was thought to be a myomatous uterus, a stage IIB squamous cell carcinoma of the cervix was discovered and transected during the procedure. In this case the consultant should have recognized the true nature of the problem at his examination.

Physicians do not use consultation enough, as pointed out in this study. Many gynecologists need consultation in managing patients with malignant disease; they may not be staging according to most recent methods or providing adequate pretreatment evaluation and posttreatment follow-up. Some physicians, general radiologists, and radiotherapists are treating cervical malignancy without adequate coordination with a gynecologist or gynecologic oncologist. Failure to coordinate care in this way may result in inferior treatment, if the possibility of surgery is excluded or if adequate irradiation cannot be given. An occasional patient with a narrow vagina or cervical stenosis, or both, may need a gynecologist's practiced hand to insert the intrauterine radium applicator.

Primary therapy should be optimum for all patients with all stages of disease. Patients who are unable to tolerate therapeutic doses of radiation or to withstand the necessary radical surgery or whose disease has progressed to an advanced stage may constitute a group that cannot be cured. A few patients with carcinomas that are very aggressive, rapidly growing, and resistant to therapy may also be called unavoidable deaths. However, it appears from this study that optimum therapy can reduce the number of deaths and cases of persistent disease. Optimum therapy includes high-energy external beam therapy, such as cobalt or linear acceleration combined with optimum radium distribution using techniques that allow computerized dosimetry, so that acceptable dosages of radium therapy to points A and B can be accurately measured, or expertly done radical hysterectomy by an experienced gynecologic oncologist.

Posttreatment follow-up of patients with cervical cancer must be done by physicians familiar with the variations in posttreatment findings among patients who have undergone radical surgery or irradiation therapy. It is desirable that the same doctors examine the patient at regular intervals after therapy, so that pelvic findings can be evaluated on the basis of previous examinations. Any change in the Pap smear or in the pelvic or physical findings demands immediate attention and evaluation by biopsy or Xray, or both. Multiple vaginal and cervical biopsies can locate the areas of epithelial abnormality and identify its extent. If present, recurrence can be treated as early as possible. Radical and ultraradical surgery performed early in the course of persistent or recurrent disease can be curative in many patients. Some patients were denied the possibility of a secondary cure because the primary physician assumed that persistent or recurrent disease was incurable and did not refer the patient for radical or ultraradical surgery.

There are many opportunities to improve the survival of patients with cervical cancer: through earlier diagnosis and treatment, better screening and diagnostic methods, optimum primary therapy, more careful follow-up, and earlier retreatment by experienced and knowledgeable oncologists, when indicated. The deficiencies in management uncovered by this study should point out to all physicians how the prognosis for patients with cervical carcinoma can be improved.

In short, our data indicate that patients with cervical carcinoma should be referred to a treatment center where expertise is available in all aspects of management. This may not guarantee a cure, but at least the patient will have the benefit of the latest concepts in evaluation and of all treatment modalities provided by physicians who devote all or most of their time to the treatment of gynecologic cancer.

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Pt.2, May 1979

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New Directions for Health Care

Report and Recommendations
of the Minnesota Medical Association's
Commission on Health Care Costs
1979

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Table of Contents

Preface vii
Executive Summary ix

Introduction 1

1/ Spiraling Health Care Costs — A Problem of Incentives 3

2/ The Two Alternative Strategies for Positive Change 9

3/ The Commission's Decision and Their Fundamental Recommendations 13

Recommendation 1: Organize New Health Care Plans 13
Recommendation 2: Promote Market Forces 13
Recommendation 3: Eliminate Barriers to a Competitive Marketplace 14
Recommendation 4: Institute Cost-Sharing 15

4/ Recommendations Directly Affecting Incentives 17

Recommendation 5: Utilization Review 18
Recommendation 6: Second Surgical Opinions 19
Recommendation 7: Feedback for Physicians 19
Recommendation 8: Hospital-Based Physician Compensation 19
Recommendation 9: Health Promotion by Physicians 20
Recommendation 10: Health Promotion by Industry 20
Recommendation 11: Health Promotion by Third Party Payers 21
Recommendation 12: Length of Stay 21
Recommendation 13: Treatment Modalities 22
Recommendation 14: Clinical Practices 22
Recommendation 15: Graduated Levels of Care 23
Recommendation 16: Preadmission Testing 23
Recommendation 17: Emergency Room Utilization 24
Recommendation 18: Emergency Room Practice 24
Recommendation 19: Hospital Capacity Reductions 24
Recommendation 20: Reducing Capacity in Rural Areas 25
Recommendation 21: Financial Compensation for Closure 25
Recommendation 22: Revising Hospital Rate Structure 25
Recommendation 23: Medicare/Medicaid Reimbursement 26
Recommendation 24: An Information Clearinghouse 26
Recommendation 25: Hospital Boards 26

5/ Recommendations Aiming at Cost-Effective Behavior 29

Recommendation 26: Desirable Practice Patterns 29
Recommendation 27: Medical School Curricula 30
Recommendation 28: Clinical Reviews and Case Presentations 30
Recommendation 29: Board Examinations 30
Recommendation 30: Continuing Medical Education 31
Recommendation 31: Cost-Effectiveness in Audits 31
Recommendation 32: Laboratory and Radiology Use 31
Recommendation 33: Cost-Sensitizing 32
Recommendation 34: Health Promotion Task Force 32
Recommendation 35: Health Status in School-Age Children 33
Recommendation 36: Obtaining Primary Providers 34
Recommendation 37: Self-Care for Consumers 34

6/ Recommendations to Improve the Cost-Effectiveness of Government Regulation 35

Recommendation 38: Government Regulation 35
Recommendation 39: Certificate of Need 36
Recommendation 40: Allied Health Providers 37

7/ Implementing The Commission's Recommendations 39

Recommendation 41: Health Care Coalition 39

Footnotes 40
Appendix A: Biographical Notes on Members of the Commission 40
Appendix B: Text of the Recommendations 41
Appendix C: Dissenting Comments 45
Appendix D: Selected Readings on Issues Discussed in this report 45

Preface

In May, 1977, the Commission on Health Care Costs was convened by the Minnesota Medical Association to study and discuss the now well-rehearsed problem of rapidly rising health care costs. We in Minnesota are by no means beginning from scratch in addressing the problem: There are some commendable corrective activities occurring on a voluntary basis within the state even now — sharing of hospital services, efforts of the Ad Hoc Committee of the Minnesota Medical Association to explore alternative modes of health care delivery, extensive efforts in health planning throughout the state, the state's hospital rate review program, and others. Furthermore, Minnesota has led the nation in the development of Health Maintenance Organizations (HMOs) — health care plans that are introducing competition into the health care marketplace — and Minnesota leads the country in the promotion of Family Practice specialization in medical schools and rural preceptorships as potential remedies to the problem of physician maldistribution. Thus, the Commission's work took place within the context of a progressive and sophisticated state medical community.

A wide range of viewpoints and expertise was presented on the 21-member Commission (see **Appendix A** for biographical notes on the members). Participants were drawn from both labor and industry, from the provider as well as the institutional community, and from the third party payer community. Although staff support was supplied by the Minnesota Medical Association, the material presented in this report is independent of and not influenced by this organization.

Early in its deliberations, the Commission divided into four task forces to consider in depth each of the following specific components of health care delivery that impact costs: (1) the provider; (2) the consumer; (3) the institution; and (4) the third party payer. The charge of the task forces was to develop recommendations and present these to the Commission as a whole for adoption. (The text of the final recommendations appears in **Appendix B.)** When Commission members dissented from a recommendation adopted by the group as a whole, they were given the opportunity to prepare dissenting comments. Such recommendations are identified in the text by a double asterisk (**) and the dissenting comments can be found in **Appendix C.**

In attempting to make recommendations that could achieve the goal of cost containment, the various task forces agreed that the recommendations had to recognize certain constraints:

- No recommendation should result in a Minnesota resident being denied adequate or timely care because of inability to pay.
- No recommendation should restrict access to care unnecessarily on any basis (income, locations, race, etc.).
- No recommendation should have the effect of reducing the quality or effectiveness of the health care delivered within the state.

Within these constraints, the task forces had total freedom to devise whatever they felt would be effective strategies for containing costs.

The Commission's work was focused on the health care system in Minnesota, but since the state is, of course, not an island unto itself, many of the recommendations address national issues and are framed within the national context. In particular, the Commission would like to stress the recommendation for formation of a "Health Care Coalition" (Recommendation 41), as this type of cooperation could well serve as a model to the rest of the nation of what the private sector can do on its own, independent of government support and regulation. Implementing the recommendations will undoubtedly be difficult because they cut across the parochial interests of providers, organized labor, institutions, insurance companies, and others. Each group will have to make some concessions for the benefit of society as a whole. This is where the real work of the proposed Health Care Coalition could well come in — negotiating concessions and agreements among divergent interest groups. It is hoped that the recommendations at the very least will spur discussion and lead to change, not just within the State of Minnesota, but across the nation as well.

Executive Summary

Health care costs are inflating at an alarming rate and thus have become a matter of wide concern. The Minnesota Medical Association formed a Commission on Health Care Costs in May, 1977, to study the cost situation and to develop recommendations that might mprove it.

The cost rise is being caused by many factors, the most mportant of which are the *incentives* operating within the health care system. They are "abnormal" incentives for an economic system, for they serve to bring about wasteful behavior rather than the cost-conscious behavior molded by the incentives in most markets.

Specifically, none of the groups making up the health care system — providers of services, consumers of services, institutions, or third party payers — have the ncentive to consider costs when making health care choices: Providers have incentives to overtreat — to do all hat they can regardless of costs; consumers have the ncentive to seek all the care they can and aren't concerned with costs, since insurance covers most expenses; institutions have the incentive to overserve and to provide more and more expensive facilities to attract doctors; third party payers have the incentive to provide wider and wider coverage in response to demand. None of these groups is acting maliciously; they are behaving rationally given their incentives. However, heir behavior serves to drive costs up in the health care ndustry rather than to hold costs in check as it would in a cost-conscious industry. Clearly, something has to change to alter this vicious circle.

Two alternative strategies are available that could potentially control costs in the health care system:

— **expansion of government regulation** to all areas contributing to cost rises (a system changed through *outside* forces)

— **stimulation of competitive forces** through creation of a pluralistic delivery system (a system changed from *within)*

The Commission on Health Care Costs decisively adopted the latter alternative as the more desirable direction to take, a position similar to that of the AMA.

The actions considered fundamental by the Commission to actualize this pluralistic, market-oriented system are:

Organize new health care plans which vie with the traditional delivery system for consumers (HMOs are the most common type of health care plan now in operation, but the plans could take a variety of forms).

Promote market forces through making health care plans widely available to employees, Medicare/Medicaid recipients, and the self-employed.

Eliminate barriers, legal and otherwise, to a competitive health care marketplace.

Include cost-sharing in insurance plans and health care plans (if included in the price of premiums, cost-sharing could be used to encourage employees to enroll in cost-effective plans; if included in the costs of actual services, it should serve to reduce unnecessary use of these services).

The Commission adopted 36 other recommendations that either expand upon or support these fundamental recommendations. They fall into three general categories:

Recommendations directly affecting the incentives of the different groups involved in the health care system. Actions suggested are mechanisms such as utilization review and second surgical opinion programs to alter *physicians' incentives;* encouragement of more healthful lifestyles to modify *consumers' incentives;* reducing overtreatment, substituting lower-cost for high-cost treatment modes, revising rate structures, and reducing excess capacity to change *institutions' incentives;* and making multiple choices of health care coverage available to consumers to make *third party payers* compete.

Recommendations aiming at cost-effective behavior. These actions would hopefully raise cost-sensitivity in *physicians* — both those in training and those already in practice — by, for example, including cost-considerations among the subject matter taught in medical school and continuing medical education courses, and including cost-effectiveness in audits of medical quality. Actions recommended to raise cost-sensitivity in *consumers* include undertaking a well-coordinated strategy of health promotion, improving health education in schools, and training consumers in the wise and cost-effective use of the health care system.

Recommendations to improve the cost-effectiveness of government regulation, for which the cost of complying is now only driving costs up still farther. Suggestions in this area are centered around two topics — making certificate of need regulations more equitable and dealing more carefully with allied health professionals as far as licensing and reimbursement.

- The Commission's final recommendation calls for formation of a Health Care Coalition, a body charged with implementing the suggested actions. A major challenge facing this group would be to bring together the diverse interests of the different factions affected by the recommendations, factors which would each have to make certain concessions for the benefit of society as a whole. If successful, the Coalition could well serve as a model for the rest of the nation of what the private sector can accomplish on its own, independent of government regulation, to improve the system's performance.
- It is the Commission's hope that their work will spur discussion and lead to positive change in Minnesota and across the nation.

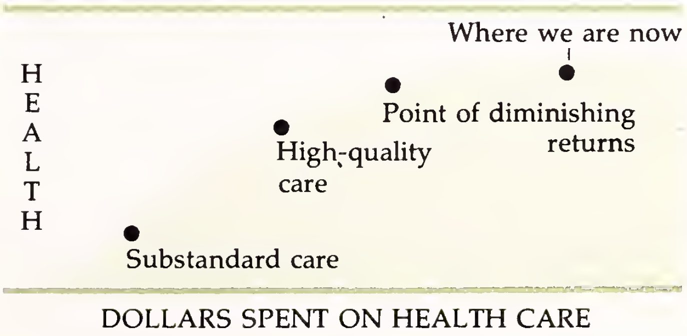
Introduction

This report from the Minnesota Medical Association's Commission on Health Care Costs presents the results of 18 months of study and discussion by experts in many fields on the problem of escalating health care costs. The first chapter lays the foundation for the Commission's recommendations by exploring the underlying causes of rising costs in the health care industry. The next chapter investigates the two broad strategies that might be undertaken to deal with these underlying causes. Chapter 3 presents the Commission's decision as to the best strategy to follow and presents their fundamental recommendations from specific recommendations in two general areas. The next three chapters include 36 recommendations that directly affect incentives, that aim at cost-effective behavior, and that focus on improving government regulation. Chapter 7 gives the Commission's final recommendation for a method of implementing the suggested actions.

The last twenty years have brought dramatic improvements in the quality of care and the range of services that the health care delivery system can provide. Hip joints can be replaced, cholesterol-clogged arteries can be bypassed, hypertension can be treated by more effective drugs — the list goes on and on of new, beneficial drugs, surgeries, diagnostics, and therapies. But along with the new and improved services have come dramatic increases in costs, with paradoxically little attendant improvement in health, at least insofar as measured by life expectancy: A 40-year-old male could look forward to 31.2 more years of life in 1900, compared with 31.7 more years in 1970 — a remarkably small increase for 70 years of great technologic advances. However, from 1970 to 1976 there has been an increase of approximately five years of life expectancy. This appears to be due primarily to behavioral changes in smoking and nutrition along with more rigorous treatment of hypertension.

From an economic perspective it would seem that we have passed the point of diminishing returns (see **Figure 1**). Our exact location on the curve could be the subject of considerable debate, but there is little argument that the dollars spent now on health bring comparatively little benefit in terms of the general public's health status if we compare those dollars with the dollars spent in the first 50 years of the century — even after adjusting for inflation.

Figure 1. Conceptual view of health care expenditures compared with returns in health



The decline in returns has no doubt been partially caused by the shift from infectious to chronic disease. Infectious diseases such as diptheria, smallpox, and polio can be dealt with by measures such as better sanitation and widespread vaccinations. These are comparatively inexpensive methods of intervention compared with the sophisticated therapies and long-term care that are frequently undertaken in victims of stroke and heart disease, arthritis, and cancer.

It is probable that these now-common chronic diseases are in large part caused by environmental pollution and changes in lifestyle (diet, exercise, chemical use, etc.). At first glance, it would seem that behavioral and environmental interventions would have the greatest potential for reducing disease and consequently reducing the cost of treating disease. However, there are some fundamental reasons why this type of intervention is unlikely to take place: The state of the art in the field of behavioral intervention is probably not sufficiently sophisticated to actually effect the changes that may be necessary, nor does the public seem sufficiently committed to the drastic actions necessary to clean up the environment. Perhaps more importantly, the *incentives* in the health care delivery system are not conducive to the *practice* of preventive or cost-effective medicine among providers of care or to cost-effective health care *choices* among consumers of services.

What exactly does cost-effective health care practice or choices mean? Health care decisions always involve alternatives, and choices are made depending upon factors such as how unlimited resources are, how highly life is valued, how highly the quality of life is valued, and how serious the effects of disease are. Our society has been making health care choices as if the resources were unlimited. We have, in effect, been behaving in this particular marketplace without thought to cost, and this behavior is causing costs to inflate rapidly.

Because we can no longer pretend that our resources are unlimited, we must face the fact that constraints will eventually force us to carefully scrutinize the benefits we gain for the amount we expend. We must strive to gain the most health for the least resources by asking questions such as these: Could we gain more benefits in health status if we used our resources differently? Could we benefit more people if health care were managed differently? Could we achieve more "health" or receive the same health benefits if the methods of delivering care were more efficient and more cost-effective?

The Commission believes that cost-effective behavior will occur in the health care system only if *incentives* exist to practice and purchase health care cost-effectively. Such incentives are obviously now lacking in our system. It is our present faulty incentives which will be examined in greater detail in the following section, and to which most of the Commission's recommendations are addressed.

Chapter 1

Spiraling Health Care Costs — A Problem of Incentives

The Commission on Health Care Costs studied the subject of incentives in great depth. The rationale for this focus is twofold:

- Incentives shape the performance of a system and the behavior of the people functioning within it.
- If a system's incentives are changed, the system's performance is changed.

Both of these points seem obvious, but their implications are profound. An important implication of the first point — that incentives shape a system — is that, although the people in a system do control that system, they *do not act independently* — they are *controlled* by the system's *incentives*. Thus, value judgments, such as "Doctors are money-hungry," or "Hospitals are sloppily run," are unfair and irrelevant in an analysis of the health care system's problems. Any system given the same incentives would function in the same way, and the people in it would behave in the same way: If the school system had the same built-in incentives as the health care system, we would now be addressing the issue of containing costs in education and criticizing teachers for their exorbitant salaries.

The other important implication of the first point is that, if a behavior persists, it must in some way be obtaining reinforcement through the incentives operating in the system — no matter how contrary this behavior might be to logic and rational analysis. For example, because economic studies have ascertained that this country has an excess number of hospital beds, it would seem to make considerable sense for some hospitals to combine services with others — e.g., for one hospital to handle only obstetrics-gynecology cases and another to take the pediatric service.

Yet this does not often happen, and the reasons for it will become clear when the incentives under which hospitals are operating are examined later in this chapter. In trying to understand why a given behavior is occurring, ask these questions:

- What are the "payoffs" for the current behavior?
- What would be the likely consequences if the behavior were to change?
- Is something negative avoided by the current course of action?

If a behavior persists in a system, it is safe to conclude that the behavior facilitates survival of the system.

The implications of the second point — that if incentives change, then a system will change — are most important in terms of trying to improve a system in general and in making recommendations to improve the health care system in particular. The implication is that a system can be changed from within by altering its incentives and without outside "tinkering."

In the health care industry, it is wasteful behavior on both "buyers' " and "sellers' " parts that is driving costs up. And this behavior persists. Thus, this behavior — *wasteful* behavior — is somehow being rewarded in the health care system. This is unlike most "normal" marketplaces, where efficient, rather than wasteful, behavior is rewarded and persists. Several factors in the health care marketplace underlie its "abnormal" incentives:

- Technology and expertise within the medical profession itself continue to expand — doctors are able to do more and more with more and more expensive equipment.
- Third party coverage, which not only covers the expenses of expansion in technology and services but also provides "first dollar" coverage for medical services and thus only nourishes consumer demand, has become common.
- Government regulation has increased in response to the rise in costs caused by the first two factors, but has in fact itself become a contributing factor to the rise in costs.

Several groups are affected by these factors and respond to the resulting incentives in the way that makes sense for them — no matter how their behavior may drive up costs:

— **providers** — primarily physicians who deliver and order health care services, although all allied health providers would be included in this group (in this report "providers" refers mainly to physicians)

— **consumers** — the self-employed who buy their own insurance; employers who purchase group policies, and employees, including labor, whose demands for particular benefits shape the health care plans they receive ("consumer" refers to both the sick and the healthy purchaser of services)

— **institutions** — hospitals, outpatient clinics, extended care centers, etc. (in this report, "institution" refers primarily to acute care facilities, i.e., hospitals)
— **third party payers** — insurance carriers, Blue Cross/Blue Shield, Health Maintenance Organizations, the government in its role of underwriter for Medicare/Medicaid benefits, and employers who self-insure their employees ("third party payers" in this report refers primarily to traditional insurance carriers)

In some instances incentives for different members of one group may vary: For example, HMOs frequently have different incentives than insurance carriers even though they can both be considered "third party payers"; labor and management have diverse and sometimes conflicting incentives although they are both "consumers"; and the government's incentives are quite distinct from insurance carriers' incentives though both are "third party payers." For the purposes of this report, the predominant incentives of a whole group will be characterized and the minority "positions" ignored — unless they actually influence the operation of the system in some manner. Again, each of these groups responds to the incentives with which it is faced. None of the groups is to blame for the system's problems; each is behaving rationally given its incentives.

Provider Incentives

The incentives under which providers operate drive them *to do more and more technical procedures and to be simultaneously less and less sensitive to cost.* This occurs because medicine is not an exact science and the human body is wonderfully complex. Tests to diagnose what is happening within it are only accurate at certain levels. Subsequent tests may aid in pinpointing specific conditions, but may also be unreliable. When deciding upon therapies, there are not clear procedures or rationales for undertaking one course of action or another. Each course, be it operation, drug regimen, or other therapy, has a certain probability of success, certain limitations, and certain complications that may arise. Good medicine is largely a matter of good judgment in evaluating the probabilities of the most effective treatment for a particular patient. And good judgment is dependent upon good information.

The search for good information, plus the ethical responsibility to his or her patient, creates an incentive to *do more* — it leads the physician to conduct test after test to make sure a diagnosis is accurate and, when the diagnosis is established, to treat in as maximal a way as possible. The physician has, after all, spent years learning to do the most and the best that he or she can do for patients. The impact on the health care system of trying to do "all that is possible" is that more and more tests are developed that yield more and more information at greater and greater cost. Moreover, more and more cases are treated that were formerly untreatable and perhaps still are. If the technology exists to do a certain procedure, why not do it, regardless of its demonstrated effectiveness? So, the incentive to test without restraint and to treat without demonstrated effectiveness is operating with an absence of any balancing incentive to be mindful of costs.

The reason for the absence of any balancing incentive to practice efficiently is widespread third party health care coverage. This serves to remove any incentive from physicians to be sensitive to the costs of their diagnostic and treatment procedures. They needn't worry about their patients' ability to pay since most costs are reimbursable. Furthermore, billing and reimbursement are handled so automatically, particularly in a hospital, that physicians often have no idea what the charges are for the services and materials they order. Since there is little awareness of charges, there is little incentive to stop treating, even when it becomes apparent there is no gain from further treatment. Indeed, because there is little sensitivity to cost, there has been little cost accounting on which to base fee structures. Fees may be arrived at by approximation and set arbitrarily in proportion to the service rendered, with no one asking, "Just how was this particular fee arrived at?"

A second incentive operating for a physician is the incentive *to gain the respect of one's peers*. The development of new procedures, technologies, and treatments, and mastery of challenging and delicate procedures are as highly regarded in medicine as they are in other fields. Clearly, it is more "interesting" to do the complicated and challenging than it is to do the simple and mundane. Furthermore, higher fees can be charged for specialized and complicated services. As a result, specialties and subspecialties proliferate, the fees associated with these specialties increase, and the technology that is associated with them is overutilized.

Finally, one more incentive exists and that is the incentive *to protect oneself from malpractice suits*. This perhaps has more influence on physicians practicing in an Emergency Room because they frequently function under two major disadvantages: the pressure to take immediate action and the ignorance of the patient's medical history. As a consequence, procedures tend to be overly elaborate and may be undertaken to provide a basis for a good defense rather than out of strict medical necessity.

None of these incentives is peculiar to medical professionals. Any group of individuals operating with these incentives would function in the same way. Indeed, except for the actual *dis*incentive to be concerned with costs, most of the incentives are laudatory and bring about the exact behavior that we, as a society, expect and demand of a highly selective, highly ethical, and highly skilled group who are responsible for making life and death decisions.

Consumer Incentives

Consumers make choices in the health care system based on *minimizing their costs* and *obtaining all the services* that might contribute to their personal health. In times of good health, a consumer's behavior tends to be controlled by short-term rewards — the immediate gratification obtained through smoking, drinking, and eating high calorie, high fat foods, for example — while the long-term effects of ill health have little effect on present behavior. There is no "charge" for unhealthful behavior patterns: Those with healthful lifestyles pay the same health insurance premiums as those who live "unhealthfully." Moreover, people are usually not refused work based on whether they smoke or drink, even though these habits have been shown to cost employers tremendous amounts in lost worktime and medical expenses. Thus, too little incentive exists for anyone who is not actually sick to adopt a different, safer, more healthful lifestyle.

When one does become sick, the incentive is *to regain health as quickly as possible* and *to spare no expense* in doing so, particularly if the expenses will be reimbursed by third party health care coverage. Here the providers' and consumers' incentives coincide: The consumer is usually willing to do anything that might be remotely useful and the provider has an incentive to treat maximally, without regard to cost. Hence, both groups have incentive to overuse high-cost technology, institutional care, and elective surgery.

When care is required, consumers have the incentive *to limit their use of those services for which they will have to bear the costs and to instead use services that are reimbursable under their insurance plan.* For most people, this means that extra days in the hospital are "better" financially than outpatient testing or early release to home or to an extended care facility where full or even partial coverage of these associated expenses is often not available. The end result is a considerable number of extra acute-care hospital days that do not have to be paid for directly by consumers, but that all consumers end up bearing financially, although in a diluted form.

Finally, there is an incentive operating from a *tax perspective* to overuse services. The tax law has long encouraged employers and employees to buy group insurance with low deductibles — "shallow" coverage — so that routine medical bills can be paid for with untaxed rather than after-tax dollars. Economist Martin Feldstein has estimated that a typical wage earner can purchase nearly 50% more health care services for the same money in this manner.[1] The result is that consumers are often overinsured against routine expenses. The expansion of coverage to dental benefits is a result of this type of tax incentive.

Institutional Incentives

Hospitals in some sense represent a given community and in a very real sense reflect on the public image of a community: That an area has the "biggest" or the "newest" or the "best" serves as a drawing card in competing with other hospitals and other communities. Besides, the quality of a community's hospitals is an indication of how that community serves its people. Because of civic pride and favorable loan treatment brought about by the Hill-Burton Act of 1946, we as a nation have built new hospitals and additional wings to old ones at a fast rate.

As a consequence of this building "boom" the nation now has substantial excess capacity in its hospitals. In 1975, if entire "extra" hospitals had been closed, it would have been possible, at least theoretically, to reduce hospital expenditures by $3 billion a year or 8% of the overall annual hospital expenditures.[2] It would seem reasonable to eliminate this extra capacity, but in reality there are other incentives spurring on hospitals which directly counteract this course of action, however logical it may seem.

Certificate of Need (CON) legislation was enacted to curb the drive toward more and more hospital beds. In practice, it has had the opposite effect: Hospitals must have income in order to survive, and the way to get income is through receipt of payments for beds and services. Thus, reduction in beds is the equivalent to a reduction in income. Since CON licenses the number of beds on the basis of occupancy rates, the legislation generates an incentive *to maintain or add to the number of beds* in a given hospital and *to keep the occupancy rate as high as possible* in order to avoid losing the number of beds presently licensed. Consequently, hospitals exert little pressure on physicians to reduce patients' lengths of stay. Indeed, there is active *encouragement* of institutionalized care.

Another incentive not to reduce the number of beds arises from the *tax treatment* of hospitals and third party coverage, both of which are built around acute-care beds. Because non-acute-care beds are reimbursable at a lower rate or nonreimbursable, there is no incentive to convert beds to other uses — regardless of the needs of the population. The result of this incentive is that we have too many beds in acute care, Intensive Care Units, and Coronary Care Units, and not enough beds in extended care and other areas requiring lower cost services.

It is physicians, not patients, who are really the clients of hospitals, since physicians are the ones who generate the patients who in turn generate the income. Wooing physicians thus becomes a main task of any hospital and provides a strong incentive *to have the things at hand that physicians want:* sophisticated laboratories and the newest and best equipment available. As a result, we have a proliferation of expensive technologies, nuclear medicine, CAT scanners, therapeutic centers such as Coronary Care Units and Intensive Care Units, and various diagnostic technologies — all far in excess of what is actually required by the population. And, there is no incentive to share these technologies and services, since each hospital is competing with other hospitals for physicians and for income.

A final "abnormal" incentive is that, unlike most private industries in which income is based on reducing costs and thus increasing profits, hospitals are reimbursed on the basis of their costs. This gives them no incentive to reduce costs but only *to generate more.* In addition, costs are determined by the hospital administrator. The net effect is that costs always go up or at least remain the same in order to maintain the cost basis on which rates are determined.

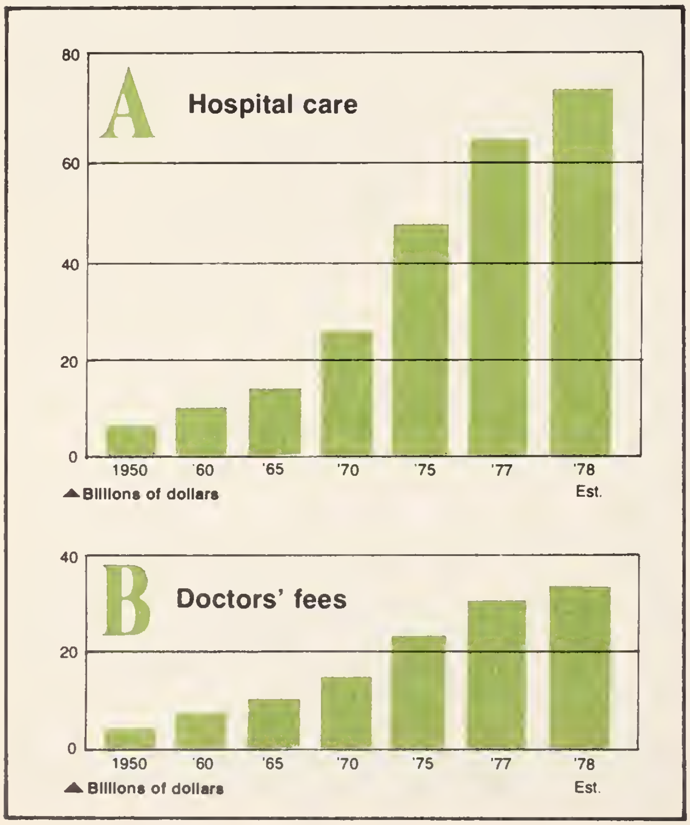
Third Party Incentives

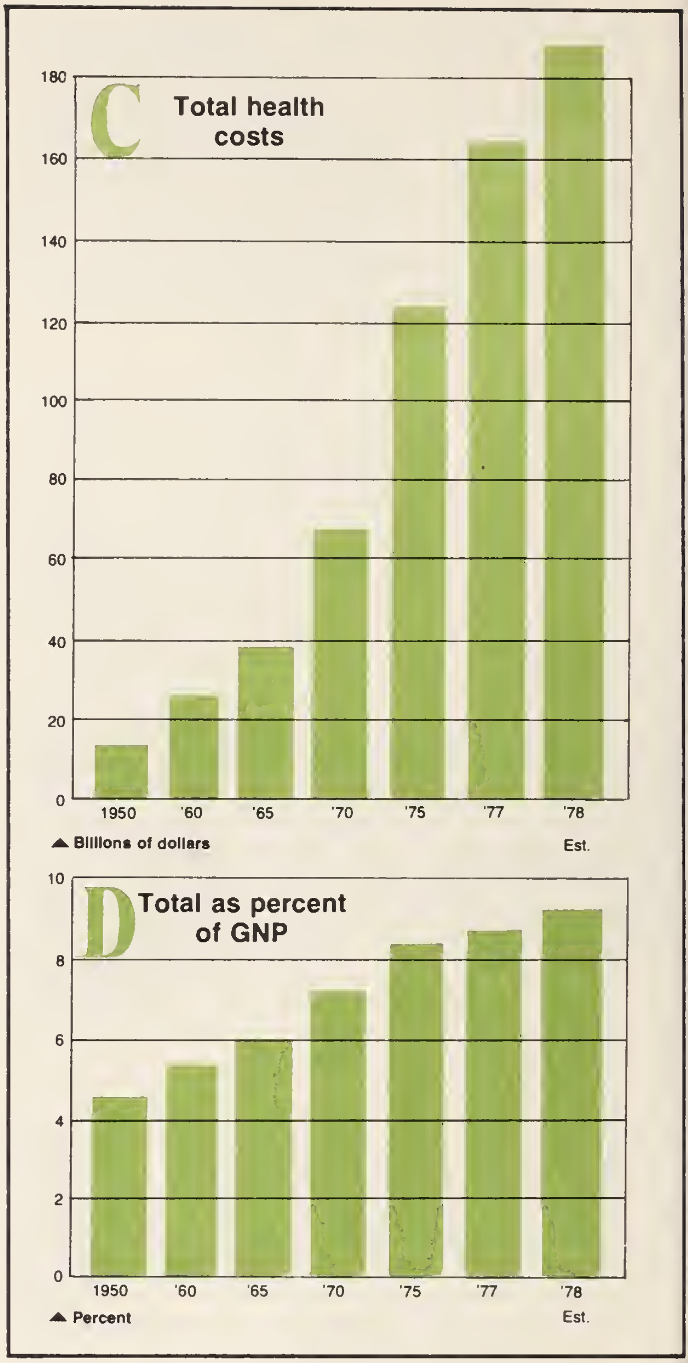
Third party payers share an incentive with institutions in that their reimbursements are based on costs incurred. Because most premiums are experience-rated, the higher the costs of health care, the more premium dollars are generated. Since third party payers are often paid on a cost-plus basis, they have no incentive to be concerned with the number of health care services purchased or with the costs of those services. The only incentive that exists for this group is to identify and avoid fraudulent claims.

The Impact of These Incentives

The impact of all of these incentives on health care costs has been dramatic (see **Figure 2**). Hospital care consumed $3.7 billion in 1950; in 1977 the charges were $65.6 billion. Doctors' fees went from $2.7 billion to $32.2 billion in the same period, and total expenses for health care went from $12 billion to $162.6 billion. The percentage of GNP devoted to health care has nearly doubled from 4.5% to almost 9% and it is estimated that health care costs could approach 10% of the GNP by 1983. We presently spend more on health care than we do on energy.

Figure 2. Cost increases in:(a) Hospital care; (b) Physicians' fees; (c) Total health care costs; (d) Total as percent of GNP





Source: Social Security Bulletin (April, 1977), Council on Wage & Price Stability (March, 1978)

The enormous amount of money spent on health care can be appreciated by comparing the expenditures in the industry to those of other services. The Consumer Price Index gives us a picture of how medical care compares (see **Table 1**). It is clear that the rate of increase in prices for all services has outstripped the rate for other goods by 52% and medical care has far outdistanced the other services with a 30% faster rate of increase. Even in comparison with other rapidly increasing prices for services, then, health care has the dubious honor of leading the pack. It should be recognized, however, that the rapidly expanding technology in the medical field has altered both the nature and intensity of services to a far greater extent than exists in other service areas.

Table 1. Change in Consumer Price Index by commodity and service group, using 1967 as the base year (100)*

	1950	1960	1970	1977	Percent Increase Between 1950-1977
All Items	72.1	88.7	116.3	181.5	152%
All Commodities	78.8	91.5	113.5	174.7	122%
All Services	58.7	83.5	121.6	194.3	231%
Services Less Rent	56.0	81.9	123.7	201.6	260%
All Health Care Services	49.2	74.9	124.2	216.7	340%

* *Data is based on urban wage earners and clerical workers so does not reflect rural experience.*

Source: Data derived from Tables B-50 and B-51 in the Annual Report of the Council of Economic Advisors. Washington, D.C.: Executive Office of the President; 1978.

Up to this point, only the nation as a whole has been considered, but it would be valuable to investigate how Minnesota compares with the nation as a whole. Except for hospital data, there is little to go on, but what data there are suggest that little difference exists between Minnesota and the rest of the nation in terms of rate of increase in costs in the health care sector. Minnesota does show anomalies in its delivery system which reflect the fact that Minnesota exports care to the region and the nation. In addition, the relatively widespread existence of HMOs in the metropolitan area *is* bringing about competition in the health care sector. In spite of these fairly unique characteristics of Minnesota health care, however, in terms of occupancy rates, use of outpatient facilities, and rates of increase in expenditures, the state is no further ahead than the nation as a whole.

Where Are We Headed?

Where are all of these expenditures and incentives leading? One way to answer this is to project the rates of increase and see where these rates take us (see **Table 2**). It appears that the hospital sector alone will eventually consume all of the GNP if it continues at its present rate of growth: All of the population will either be in a hospital bed or ministering to someone in a hospital bed at some not-too-distant point in time. This is obviously a *Reductio Ad Absurdum* argument, but it does point up two things:

- If society allows the present rate of increase to continue, other parts of society will suffer. Where will the money come from for education, new energy technologies, defense, or conservation of natural resources, for example?
- Since it is unlikely that society will choose to let this happen, the health care delivery system *must change.* The question is: *How*?

Table 2. Hospital sector share of gross national product

Year	Estimated share at 5% per annum increase (%)	Estimated share at 7% per annum increase (%)
1980	4.34	4.76
1985	5.54	6.69
1990	7.07	9.38
1995	9.02	13.16
2000	11.51	18.45
2005	14.69	25.88
2010	18.75	36.30
2015	23.94	50.96
2020	30.55	71.41
2025	38.99	100.15
2030	49.76	
2035	63.51	
2040	81.06	
2045	103.45	

Source: Dahl, Tor: Containment of Health Care Costs – the Case in Minnesota. A report to the Health Care Cost Commission of the Minnesota Medical Association; December 13, 1977.

The next two chapters of this report will address the general strategies that might be adopted to change the delivery system, as well as the specific strategies for change adopted and recommended by the Commission.

Chapter 2

The Two Alternative Strategies for Positive Change

Various strategies have been proposed to remedy the problems in the health care system, but they all come down to two essentially divergent and contradictory approaches:

- — command-and-control regulation
- — restoration of market forces in the medical marketplace

COMMAND-AND-CONTROL REGULATION

Government regulation is not monolithic — one regulation after the next, the only difference being the subject matter — as it is often imagined. Rather, there are at least two types of regulation. One is market-corrective regulation. Its purpose is to maintain market forces in industries where they are already present and to correct conditions inhibiting market forces or restraining trade; it does not control entry into a market. The Federal Trade Commission is an example of an agency promulgating this kind of regulation.

The other type of regulation — the one that we are referring to as "command-and-control" regulation — essentially *supplants* market forces. It controls entry into a market, sets the prices of goods or services within the market, and allocates resources within the marketplace. This kind of regulation arises when the market forces in a given industry are absent or weak, as they are in the health care system. Certificate of Need legislation, Professional Standards Review Organization (PSRO) legislation, health manpower regulations and funding, and Medicare/Medicaid regulations all represent command-and-control regulation — they aim to fill the vacuum created by the absence of market forces.

The major question to consider in deciding whether or not to adopt or expand command-and-control regulation is: What impact will government regulation have on the incentives in the system?

Impact on Provider Incentives. Most of the present incentives that encourage providers to do more and charge more would be locked into place by command-and-control regulation because regulators are not sufficiently knowledgeable in the complex subject of medicine to tell a physician what he or she may or may not do. Furthermore, when government regulation attempts to control an industry, the producers tend to control the regulators: Witness the relationship between regulating agencies and the oil and gas producers, or the relationship between the Federal Communications Commission and the Bell System. The proliferation of tests, technologies, and procedures with accompanying increases in fees can be expected to continue if command-and-control regulation is chosen.

Impact on Consumer Incentives. Since government regulators would be very hesitant to interfere with a private citizen's health care choices and equally unlikely to make the consumer assume more costs than he or she is presently bearing, it is unlikely that consumers would be asked to make any changes in their present non-cost-conscious style of health care under command-and-control regulation. A more likely consequence would be highly politicized health care. The recent debate on Medicaid funding for abortions which stymied Congress for an inordinant amount of time may be a preview of what would ensue.

Impact on Institutional Incentives. Because cost-plus reimbursement (the type of reimbursement scheme under which hospitals now operate) is the normal method of doing business for the government, it is unlikely that hospitals would be given any new incentives to control their costs under expanded regulation. Furthermore, hospitals are in the same position as physicians — they are producers of medical care. Therefore, they are likely to control the regulators in the same way.

Impact on Third Party Payer Incentives. In a totally regulated environment, the only role left to the health insurance industry will be that of pay agent. Should the government take over the processing of health care claims, the health insurance industry may no longer exist. Thus, this industry has an investment in not promoting regulation.

In summary, if we look at the impact of government regulation on incentives, we see that, in general, the impact would be negative — at least from the point of view of containing costs. From the perspective of the providers — both physicians and institutions — the impact may not be all bad, however, because of the newfound control that these groups would be able to exert over the regulators.

RESTORATION OF MARKET FORCES

In comparison with the regulatory process which, though politicized, is rational and predictable, the marketplace is haphazard, its processes are undefined and frequently unpredictable, and it is largely uncontrollable. In short, it is the nemesis of planners and regulators. In attempting to solve the nation's health care problems by means of the marketplace strategy rather than by command-and-control regulation, the first problem to be dealt with is how to restore market forces to the medical marketplace. The simplest way of doing this is to develop a pluralistic system in which consumers make *choices* among conventional health insurance plans and "health care plans" (the most common of these are Health Maintenance Organizations, or HMOs, but other types exist as well). Consumer choice implies *competition* because traditional fee-for-service physicians and health care plans would have to vie for the patronage of the consumer by demonstrating their various virtues. These virtues would typically include quality of care delivered, range of services offered, and premium cost.

What are Health Care Plans?

A health care plan has three essential characteristics:

- A *group of providers* (ideally fewer than a majority of those in a given community — otherwise competition is weakened) have organized themselves into a billing unit to deliver medical care.
- These providers offer a set of health care services for a *fixed fee*.
- The consumers who enroll in the plan are committed for a *given time period* to obtain their care from this set of providers.

These characteristics distinguish a health care plan from an insurance plan, because unlike insurance, which only provides *reimbursement* for services rendered, a health care plan actually *provides the services*.

Health care plans can take several forms: Group practice HMOs are the most widespread to date; SHARE, Group Health, and Med-Center are examples. Independent Practice Associations are another type. They are a form of HMO, but allow physicians to maintain their own practices; Physicians' Health Plan is the leading example in the state. Health Care Alliances, essentially a way of rating health insurance according to the efficiency of the providers used, are yet another type of health care plan; they have not yet been tried in Minnesota. There are no doubt many other potential ways of structuring health care plans; the issue is not the particular way that a plan is organized, but rather how the competition engendered among providers affects the *incentives* in the health care delivery system. To explore what effect competition would have, it is again necessary to look at each of the groups making up the system.

Impact on Provider Incentives. Both health care plans and fee-for-service practitioners would have an incentive to keep their fees down and their services moderate in order to obtain and retain patients. A *health care plan* purchases services with its own money so its providers have considerable incentive not to waste it and to operate "in the black." Thus, health care plan providers would tend to examine technologies and procedures from the stance of, "What is the most effective for the money?" As a result, unnecessary tests and procedures and inefficient use of health care institutions would be avoided as detrimental to economic survival of the plan. For those providers in *fee-for-service* practice, the incentive would be to retain and attract new patients. In order to compete effectively with health care plans, they, too, would have to examine procedures and technologies from the stance of, "What is most effective for the money?"

Impact on Consumer Incentives. Because of the increased number of choices, a consumer in a competitive system would be able to save money or obtain more benefits for the same money by choosing a more efficient provider. Those consumers who were in health care plans would likely be encouraged by their physicians to reduce their risk factors and adopt more healthful lifestyles, since health care plans have an investment in the health of their covered population.

Impact on Institutional Incentives. In a competitive market, any excess capacity would endanger the economic survival of hospitals, so they would have an incentive to maintain only the necessary number of beds and to use their existing facilities in the most efficient manner. Also, in order to obtain a stable and predictable patient flow, hospitals would have an incentive to compete with other hospitals by offering desirable rates and service packages. Finally, hospitals would be "pressured" by health care plans to operate cost-effectively and to offer volume discounts once the plans grew to the point where they had a large patient population and the resultant bargaining leverage. This situation would be considerably different from the present cost-plus reimbursement system.

Impact on Third Party Payer Incentives. Third party payers would be forced in a true market system to compete with health care plans for enrollees. This should have the impact of forcing them to pay attention to utilization patterns that drive up costs. It should also provide an incentive to keep expense ratios as low as possible in order to keep rates competitive. Third party payers would also have the incentive to compete with health care plans by forming their own health care plans (this is what Blue Cross/Blue Shield has recently done) and by selling administrative services.

CHOOSING A STRATEGY — REGULATION vs THE MARKET

The issue of which direction to take — command-and-control regulation by the government or restoration of market forces through a pluralistic delivery system — cannot be settled by simply evaluating the impact these choices may have on the incentives in the system. The issue goes much deeper than this. It is necessary first to carefully decide what things are important in the health care delivery system and what the standards are that we should work toward. The following list of standards, or goals, would probably be agreed upon as important and desirable by physicians as well as health care planners and the public:

— High quality care, with appropriate diagnoses and therapies rendered

—Clinical control by a primary provider of a given patient's case from start to finish – this would prevent oversight and duplication of effort

— Control by the primary provider over the financial expenditures involved in a case

— Accountability on the part of the primary provider for both clinical and financial performance

— Efficient operation so that costs are under control

— Sufficient flexibility to allow treatment alternatives (for example, nutritional counseling, physical fitness programs, and smoking cessation) and innovations in the manner of delivery

— Equal accessibility to all members of society

These standards by no means exhaust all possibilities for a desirable system. They focus primarily on the provider because it is he or she who directs the care and orders the services for the consumer and thus controls expenditures.

In considering which strategy to adopt — regulation or a pluralistic delivery system — it is important to determine whether the strategy chosen will work for or against each of the goals above.

The Effects of Command-and-Control Regulation on System Goals

The central thrust of government regulation will probably be to lock in whatever patterns of practice presently exist and then to resist change. This is likely because in attempting to manage a huge and complex industry serving millions of people it is undoubtedly more appealing to the regulator to leave the current modes of operation intact than to try and install new ones. The consequences on medical care would most likely be:

- *Permanent enshrinement of the present "high style" of practice in medicine as the only way to practice because of its familiarity to the regulator, its acceptability to the provider, and its political popularity with the consumer.*
- *Stifling of innovative diagnostics and therapies because the regulator would not have a convenient "pigeonhole" in which to process the new and unusual.*
- *Reduced cost-sensitivity on the part of providers: When the government gets involved in providing services, there is usually no holding back on the costs associated with delivering this service.*
- *Lack of any encouragement to be either efficient or flexible in providing or using the services of the system: Duplication of effort, conflicting regulations, and endless red tape will probably be commonplace, and novel approaches to solving problems or treating disease will probably be suppressed or slowed down because of strong pressures to maintain the status quo.*

On the more positive side, it is likely that peer review activities would be encouraged by a totally regulated system because regulators would have strong incentives to monitor patterns of practice in order to defend their actions and support their decisions. Furthermore, it is likely that access to care would be improved for all members of society.

The net effects of pursuing a strategy of government regulation would probably be increased consistency in performance on the part of providers and improved access to care. However, coupled with this would probably be a freezing of the existing perverse incentives and a slowing down or halting of change and innovation, both in the practice of medicine and in the delivery of care. It is also possible and likely that the positive effect of increased access to care would be negated by increased demand not held in check by any consumer cost-consciousness.

The Effects of A Pluralistic Delivery System on System Goals

Although all providers would ultimately be affected by a pluralistic delivery system, the system would initially affect the health care plans and only then "flow back" to the traditional fee-for-service practitioner as market forces took effect. The chief advantages of pursuing the pluralistic strategy would be enhanced clinical and financial control over cases for the provider, largely because providers would be competing with each other on the basis of performance. If providers were in a competitive position, control would be essential and they would demand it.

Since cost, too, would be a major basis of competition, it is likely that diagnostic and therapeutic procedures would be viewed with a far keener eye. Providers would likely ask: "How much am I gaining in effectiveness from this procedure? Is it worth it?" A substantial reduction in the overdelivery of care could thus be expected. Because providers in a competitive system would vie with each other on the basis of performance and price, better data would be demanded and made available to enable both primary providers and consumers to evaluate the performance of providers. Efficient providers who deliver competent care would be rewarded with stable patient populations and stable incomes. Since the focus would be on outcomes ("How well did 'X' work? How much did it cost?"), not process, innovations in treatment and flexibility in delivery styles would be encouraged. In fact, it is probable that specially tailored programs could be designed for subsets of the population since providers would have to be more sensitive to market peculiarities in order to capture the market.

Along with all of these positive effects of a pluralistic system are two major issues that are potentially negative. The first is the possibility of *underservice* – of a patient's condition being missed or treated in too minimal a way because a provider was "too" cost-conscious. Certainly, no one — most of all physicians — wants a patient to be undertreated because of cost-consciousness. On the other hand, in reality physicians are unlikely to undertreat in any environment because of the ethical responsibility they have to patients. In addition, the incentives to do a competent job would be enhanced rather than diminshed in a competitive market — all that is added is an incentive to treat rigorously and carefully rather than cost-carelessly.

A second concern in a pluralistic system is *access* to the medical market for the poor — a group at economic disadvantage in any market. Surely, this is a concern shared by all of society. There is no question that the poor would need government subsidy in order to purchase in the medical marketplace. Medicare/Medicaid is the current government response to this problem. Another possible aid would be a system of vouchers that the poor could apply to the insurance plan or health care plan of their choice — a plan consistent with the strategy of choices in a pluralistic delivery system. Overall, it seems that greater flexibility, autonomy, and quality of care would be achieved in a pluralistic environment than in a system governed by command-and-control regulation, and that the potential negative aspects of the competitive system could be resolved.

Chapter 3

The Commission's Decision and Their Fundamental Recommendations

After reviewing the arguments both for and against these alternative strategies, the Commission decisively adopted the strategy of restoring market forces in the health care system. In taking this position, the Commission is essentially endorsing the position of the AMA, which has also chosen to encourage change in this direction. A "real" health care marketplace, the Commission felt, will require two things — a pluralistic delivery system and consumer cost-sharing.

CREATE A PLURALISTIC DELIVERY SYSTEM

In order to promote pluralism in the delivery system in the state of Minnesota, the Commission felt that three major actions were necessary: to organize new health care plans, to promote fair market choices by ensuring that everyone has a chance to choose among alternative delivery systems, and to remove whatever the barriers — primarily legal and administrative — that might stand in the way of a competitive marketplace.

RECOMMENDATION 1: ORGANIZE NEW HEALTH CARE PLANS

- **Employers, insurers, providers, and interested community leaders should support the development of new and existing health care plans by providing managerial and marketing expertise — and financial support, if necessary — to providers who are forming new plans.**
- **Providers should review both the existing health care plans and proposed health care plans to identify those plans that may be consistent with their own style of practice. The Commission urges physicians to seriously consider participating in such plans.**

RECOMMENDATION 2: PROMOTE MARKET FORCES

- **Employers offering health benefits should create a fair market for health care plans by offering their employees multiple choices among conventional insurance plans and alternative health care plans. In order to insure that fair market conditions prevail among these choices, the following conditions must be met:**
  - **☐ the employer should contribute the same amount of money toward the premium of every choice available**
  - **☐ the difference between that amount and the chosen plan's actual premium should be paid by the employee or returned to him or her in another benefit form depending on whether the premium is more or less than the employer's contribution**
- **Unions should negotiate for multiple choice in their contracts to insure that each employee has individual choice of the plan best suited to his or her needs.**
- **Employers and unions should actively promote the concept of choice to employees and provide simple, comparative information about all available choices.**
- **The market and the opportunity to make fair market choices should be expanded quickly to all consumers including, but not restricted to, the groups below:**
  - **☐ Medicare/Medicaid recipients**
  - **☐ employees whose employers offer low benefit packages or do not offer health care benefits**
  - **☐ the self-employed**
  - **☐ part-time employees**
  - **☐ government employees**

RECOMMENDATION 3: ELIMINATE BARRIERS TO A COMPETITIVE MARKETPLACE

- **Competitive bidding among hospitals should be encouraged, provided that:**
  - □ **the competition is subject to the same rules as are other competitive industries and as permitted under the laws of Minnesota**
  - □ **private paying patients are not subsidizing groups**
- **Health care plans should have the latitude to design whatever set of benefits and premium charges they deem most marketable in a given employee population.**
- **Legislation and regulation that limit the flexibility of the individual delivery system should be discouraged, and existing laws and regulations that have this effect should be repealed or amended. Recognizing legitimate differences between health care plans and insurance plans, the Commission believes that laws should have an equivalent effect on the marketing of each.**

Several potential concerns should be addressed in relation to these proposed actions for promoting a pluralistic delivery system. The first has to do with protecting the employee from his or her own bad judgment in selecting a poor health care plan for his or her family's needs. If, for example, an employer offers several plans, one of which represents a low level of benefits at a very low premium (for example, a $20,000 maximum with a $2,000 deductible), an employee may choose unwisely to "play the odds" and select this option despite the fact that he or she may be financially unable to pay the deductible should illness occur.

At least two factors make this unfortunate situation unlikely to happen with great frequency, however. The first is the probable good judgment in selecting the plans to offer on the part of the employer, who has a vested interest in making sure his or her employees are not ruined financially: Any major employer is unlikely to offer an option that does not adequately cover the health needs of employees. Second, the options offered would in many cases be subject to negotiation between management and labor: Labor certainly has a vested interest in representing the interests of the employee and would be very unlikely to accept a "bad" option for consideration. Even in view of these points, a poor plan may occasionally be offered by an employer and chosen by an employee. This possibility points up the importance of clear explanatory materials that illustrate sharply the differences among the options available as recommended above, so that choices are made with full knowledge of the potential consequences.

The second issue that may come up in looking at these recommendations is: "Why should the employer pass along to the employee any savings there might be if a lower-premium plan is chosen?" At first thought, it would seem that any savings in the administrative expense of providing health care benefits should go directly to the employer. In looking at the long-term effect of such a policy, however, one will likely arrive at a different perspective: By removing the employee's incentive to choose a lower-cost plan (i.e., his or her "rebate") an employer is discouraging — or at least not encouraging — enrollment in the plan. A cost-benefit analysis would probably demonstrate that an employer would be better off in the long run to return the savings to the employee because the resultant increase in the number of employees choosing that plan would act as an incentive to all the plans offered to compete by keeping their rates down. The administrative expense devoted to health benefits would thus be either reduced or maintained at the same level as if the savings were kept by the employer in the first place, but by a slightly different route.

A final concern to address involves extending market choices to Medicare/Medicaid recipients and the "low-benefit" populations. This recommendation must be considered in conjunction with the recommendation to repeal or amend legislation limiting the latitude of health care plans, as both recommendations address the same problem. Presently, legislation requires that health care plans offer a certain level of benefits in order to "federally qualify" or to meet the mandated benefits of the State of Minnesota; this legislation in effect prevents health care plans from serving either Medicare/Medicaid recipients or low-benefits groups. Obviously, the intention behind the legislation was to protect the consumer against poor quality and bad service. But the net effect has been to restrict the choices of large segments of the population and prevent market forces from operating. The foregoing recommendations are intended to reverse this situation and give these populations the same choices as everyone else.

INSTITUTE COST-SHARING — AN INTEGRAL PART OF A PLURALISTIC SYSTEM

If we adopt a pluralistic delivery system, the impact on incentives in the system falls primarily on providers, secondarily on institutions, and only then on the consumers. Yet one of the major causes for the drastic increase in health care costs is the great demand on the part of consumers for medical care. This demand has been fueled by Medicare/Medicaid and by the first-dollar coverage promoted by the tax treatment of health insurance premiums. As a result, consumers have little incentive to be concerned with costs — they do not foot the bill, though they are, in fact, trading dollars in salary (over which they have discretion in spending) for health benefits (over which they have no control and which they may not even utilize).

In order for any market system to work, the consumer must have some incentive to be concerned with cost. In the health care market there are two points at which a consumer is potentially sensitive to cost: first, when health insurance or a health care plan is purchased; and second, when health care services are actually used. Let us consider the latter point first.

Cost-Sensitivity at the Delivery Point. The primary ways to insure consumer sensitivity at the delivery point are through deductibles, copayments, and coinsurance.

- **A deductible** is a given amount of money that must be paid before insurance "kicks in" and begins paying. *Example:* Given a deductible of $50 and a bill of $300, the consumer would pay $50, the insurance plan $250.
- **Coinsurance** means that the consumer pays a certain portion of the medical bill, usually between 10% and 20%. *Example:* If a bill were $100.00 and the coinsurance rate was 10%, the consumer's share would be $10.00.
- **A copayment** makes the consumer responsible for a certain fixed amount for a particular service, such as psychotherapy. *Example:* If a copayment were $20.00, this payment would have to be made by the consumer every time the service was rendered regardless of whether the fee were $30 or $60.

Deductibles, coinsurance, and copayments can be effective used alone, in combinations, or all together. Their function is not to shift an unmanageable portion of health care costs to the consumer, but to remind the consumer that health care is not free, that alternatives are possible, and that economic considerations should enter into decisions about health care. Ideally, whatever payment mechanisms exist, these mechanisms should do three things:

—*Encourage the consumer to utilize appropriate preventive services*

— *Cause no major financial hardship when major medical expenses are incurred*

— *Encourage cost-effective behavior on the part of the consumer, such as using his or her personal physician instead of the emergency room*

If deductibles, coinsurance, and copayments are used within these guidelines, they should have the effect of not only containing costs but improving the quality of care, since they encourage redirecting choices toward effective and efficient services.

Cost-Sensitivity at the Purchase Point. Two major mechanisms exist to increase cost-sensitivity at the time of purchasing health insurance coverage or a health care plan. The first is to ensure that the consumer has *multiple choices* among alternative insurance and health care plans, as already discussed from the perspective of implementing a pluralistic delivery system. The existence of choices puts the consumer in a position of evaluating the various benefits available and deciding whether the benefits to be gained from exercising a given option are worth the price. It would have the impact of sensitizing the consumer to the high cost of first-dollar coverage, since he or she would presumably end up paying out-of-pocket money for such coverage to make up the difference between what the employer will pay and the actual cost of first-dollar coverage.

The second way to restore cost-sensitivity at the purchase point is to eliminate or curtail the availability of secondary coverage that can be used to pick up deductibles, coinsurance, and copayments. If such coverage is available, cost-sharing at the point of delivery can be relatively easily escaped, preserving the present perverse incentives and insensitivity to costs.

Through the cost-sharing mechanisms of deductibles, coinsurance, and copayments, consumer behavior should change. Immoderate or indiscriminant use of health care services would have negative financial impact on the consumer who is sharing costs, while effective choices among competitive and efficient providers and plans would have the positive effect of minimizing the consumer's cost. Since the consumer in a pluralistic system would have free choice over which plan to purchase, the insurance companies and the health care plans involved would have the incentive to provide the best "deal" for the best price. Furthermore, the cost-sensitivity of providers might well be enhanced if their patients were to start asking questions about the price tags of various alternatives before they agreed to a course of treatment. The notion that consumers should share in the cost of premiums has already been endorsed by the Commission in the recommendation on promoting a pluralistic delivery system. In regard to additional cost-sharing, the Commission voted that the following recommendation be adopted:

RECOMMENDATION 4: INSTITUTE COST-SHARING**

- **All insurance plans or health care plans offered within the state should have cost-sharing provisions specifically directed toward discouraging immoderate or indiscriminate use of services. Cost-sharing should not, however, be a barrier to necessary therapeutic and preventive care. In addition, any secondary coverage eliminating appropriate cost-sharing should be discouraged within the state. Lastly, employees should be offered a choice of plans that utilize different amounts of cost-sharing and those differences should be reflected in the plans' respective premiums.**

Recommendations 1, 2, and 3 regarding the implementation of a pluralistic delivery system and Recommendation 4 suggesting the inclusion of cost-sharing in health care coverage represent the fundamental actions of the Commission. It is interesting to note that in some ways Minnesota has a head start in the type of system being recommended.

Minnesota — A Frontrunner in Pluralistic Health Care Delivery

The impact of a pluralistic health care system on containing costs will not be fully apparent until approximately 25% to 40% of the population of an area is

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***See Appendix C for dissenting comment.*

enrolled in some form of health care plan. Although Minnesota has not attained this goal yet, the state has led the nation in experimentation with alternative delivery systems and so is a particularly appropriate area in which to adopt a pluralistic strategy. There are currently seven HMOs operating in the state, serving 224,000 people — 11.6% of the population in the metropolitan area. Fifty-seven employers in the area offer an HMO option. This demonstrates that the Minnesota provider community is progressive and receptive to change. In fact, a large number of providers have organized themselves into an Independent Practice Association called the Physicians' Health Plan in response to the growth of the more tightly organized Prepaid Group Practice HMOs in the area. It is quite evident that market forces are emerging and being nurtured by providers in the state.

Because so many consumers have been exposed to HMOs, the level of sophistication and acceptance on the part of the public in the state — at least in the metropolitan area — is high. This sophistication is critical to the success of any marketplace because informed consumers capable of making discriminating choices are necessary to foster competition. With the flexibility of the provider community combined with the sophistication of consumers, Minnesota has an excellent base on which to build further expansion and experimentation.

The recommendations presented in the remainder of this report support, expand upon, or extend the fundamental recommendations already made. They fall into four categories:

— *Recommendations directly affecting incentives*

— *Recommendations aiming at cost-effective behavior*

— *Recommendations to improve the cost-effectiveness of government regulation*

— *Recommendations related to implementation*

Each of these categories will be the subject of a chapter in the remainder of this report. Accompanying each specific recommendation is a rationale for the suggested action or policy.

Chapter 4

Recommendations Directly Affecting Incentives

Because of the importance attached by the Commission to incentives, a considerable amount of energy was devoted to recommendations affecting these incentives. As discussed earlier in this report, each group involved in the health care system — providers, consumers, institutions, and third party payers — is affected by different incentives. Consequently, different recommendations apply to each group.

PROVIDER INCENTIVES

The recommendations that follow are concerned with two basic issues:

— *The incentive to "overtreat" patients on the part of physicians*

— *The lack of information that physicians receive on their own performance*

When a system provides incentives to behave in certain ways and gives no negative feedback on that behavior, it will — whether good or bad — increase in frequency.

The issue of overtreatment is a complex one. What is appropriate treatment in one case may be overtreatment in another, and undertreatment in still another. A considerable amount of professional judgment goes into the decision as to the level of treatment required. The patient, too, exerts certain pressures that sometimes result in overtreatment. The physician must often take into consideration factors that have little to do with the medical necessity, such as whether a recovering patient would be better off staying in the hospital because there is no one at home to care for him or her. Nonetheless, it is evident that there are admissions for procedures that do not need to be done and lengths of hospital stay that are too long. The wide variation in incidence rates for various procedures as well as the discrepancy in lengths of stay for different areas of the country give proof that considerations other than medical imperatives are often dictating behavior in the system. Several mechanisms exist that may help to equalize this situation.

Utilization Review

Generally speaking, the Commission felt that inappropriate utilization should not be reimbursed by third party payers or consumers and that the physician or the institution involved should be at risk for whatever inappropriate care might be rendered. This, however, is extremely difficult to implement from a practical standpoint, especially if the determination that care was inappropriate is made after the fact. The practical effect of retrospective refusal to reimburse is that hospitals write off the charges as bad debts which are then figured in as a part of subsequent charges. Thus, it is difficult for the consumer and the third party payer to avoid paying for inappropriate utilization.

A more fruitful approach to solving the problem is to first examine who might have the incentive to correct the problem of overservice, and second, to examine ways of preventing the problem in the first place. If we examine the health care system, it is apparent that only the consumer — and in particular the employer — has any incentive to reduce inappropriate utilization, since the premiums paid are experience-rated. Because the employer has the incentive to keep his premium levels down, he or she is in a position to exert pressure on the third party payers to insititute controls over utilization. In a sense, the employer can force the third party payer to share his or her incentive.

The consumer and the third party payer, then, have an incentive to do something about inappropriate service. There are a variety of corrective actions that can be considered:

— **Prospective Review,** in which cases are reviewed prior to admission in order to make sure a patient's condition requires hospitalization

— **Concurrent Review,** in which cases are reviewed during hospitalization and both physicians and patients are advised of the cut-off date for reimbursement

— **Retrospective Review,** in which claims are reviewed after they have been submitted and compared with profiles to determine whether they are in line with the profile, and, if they are high, to determine whether there are mitigating circumstances to justify reimbursement

The mechanisms have definite potential, but each is also accompanied by certain problems: With *prospective review* (also called preadmission screening), once a case is approved for admission, there is no subsequent check on costs; the physician and hospital can then operate as usual. With *concurrent review*, the standards for length of stay can become too rigid. All efforts are devoted to ensuring that no one goes over the time limits without good reason, but the rationality of the time limits themselves may go on unexamined. With *retrospective review*, an innocent party may be left holding the financial "bag."

With all three of the processes, there is a shared, major problem and that is the review process itself: Who does it? How are standards set? What is the appeal procedure? Minnesota has models to follow, but these models had to be carefully developed: The Physicians' Health Plan uses a simple form of prospective review. Blue Cross/Blue Shield is conducting concurrent review of all subscribers' hospitalizations. Blue Cross/Blue Shield also employs the Joint Profile System which is a sophisticated version of retrospective review designed to identify norms, unusual utilization patterns, and long-term trends. Each of these models has demonstrated cost-saving potential.

A final point to be made in regard to utilization is that the patterns of health care have developed around the lingering notion that the quantity of care is equivalent to the quality of care — in short, that more is better. In reality, this is not necessarily the case: Given an already "obese" delivery system, more is not better. One measure for the "excess fat" in the health care delivery system is the number of patient-days per 1000 population per year. The U.S. average is about 900, yet in Olmstead County in Southern Minnesota where the Mayo Clinic is located and the general level of care is extremely high, the rate is only 700, including the unemployed. Indeed, if we exclude those over 65 years of age, the rate decreases to 640.

While it is impossible to set rigid criteria for what rate of hospital utilization is "ideal," moderate rates such as those above could certainly be used as guidelines for an employer in seeking to determine whether his or her employees are higher-than-necessary utilizers. The rates should be reasonable and even generous since such a population contains only a small number, at most, of members over age 65 and because employed people usually have much lower illness rates than the unemployed. Certainly, any employer who is experiencing a rate of patient days greater than 700 per 1,000 is in a position to ask some hard questions of third party payers.

Because the Commission believed that major employers in the state could have a great impact on the utilization patterns if they chose to exercise their power, the Commission adopted the following recommendation:

RECOMMENDATION 5:
UTILIZATION REVIEW

- **Major employers in the state should exert pressure on major insurers to take steps to reduce inappropriate utilization.**

One way of implementing this recommendation might be for insurers to form an association whose task is to conduct prospective review. Physicians hired by the association would contact the attending physicians in cases of questionable hospitalization. Should there be any dispute, the unresolved issues could be sent to the Foundation for Health Care Evaluation (Minnesota's PSRO) for their opinion. Hopefully, the volume of cases actually seen by the Foundation would be negligible, since the review process should act as a deterrent.

Second Surgical Opinions

A somewhat different form of prospective review is the second surgical opinion program. This is a process in which anyone who is slated for elective surgery may have (or must have, depending on the particular program) a second opinion from a board-certified specialist. In order to ensure higher objectivity, this specialist must not be actively involved in the patient's treatment. The patient is free to follow the advice of whichever physician he or she chooses whether the recommendation for surgery is upheld or not upheld by the second physician.

The rationale for the procedure is this: The number of surgeries performed has increased over the past 10 to 15 years at a rate four and one-half times that of the population. In prepaid health care plans and in Great Britain, the rates of surgery are far lower than in the U.S. as a whole, without apparent damage to health. In spite of the fact that there are probably some justified procedures being unduly delayed in these systems, it seems clear that the incentives in our system are pushing for more and more surgery, some of which is beyond medical necessity.

The program's potential for savings may be great. A Cornell University study has investigated several second opinion programs. In a program in which second opinions were sought voluntarily, nonconcurring second opinions were given in 35% (985) of the cases. Since patients usually follow the advise of the specialist, the potential savings from avoiding the "unnecessary" surgeries was $2.25 million dollars, in contrast to the $300,000 it cost to operate that particular program.[3]

To evaluate second opinion programs fairly, however, several factors must be weighed against these impressive potential savings — the cost of deferring surgery and of alternative treatments, and the fact that some percentage of nonconfirmed patients will undergo treatment regardless of the second opinion. Thus, careful studies must continue to be undertaken to weigh the costs and benefits of this procedure. The Commission, nonetheless, believes that the potential for savings exists and therefore adopted this recommendation:

RECOMMENDATION 6: SECOND SURGICAL OPINIONS

▪ The Minnesota Medical Association should evaluate the studies done on second surgical opinion programs and monitor the results of the pilot testing presently being conducted within the state and elsewhere. Should the data indicate that either substantial cost-savings or improvement in the quality of care are possible, the Medical Association should make strong recommendations to employers and insurers that this program be adopted — possibly on a mandatory basis — throughout the state. Should the program be determined to be without merit either in terms of cost or quality, then the program should be disbanded.

Feedback on Patterns of Practice

Both utilization review and second surgical opinion programs provide disincentives to overtreat by providing a double check on the primary provider's opinion about hospitalization and surgery. In a sense, they provide feedback on performance: If a primary provider's judgments about hospitalization and surgery are continually supported by the screening physicians and board specialists, he or she knows that those judgments are on target with the best and most careful of his or her peers. On the other hand, if a physician does not receive concurring opinions from peers on a regular basis, that may suggest that his or her manner of practice is not in line with the rest of the medical profession.

The fact that utilization review and second surgical opinion programs have had an effect on styles of practice is probably not due so much to any financial disincentive that may exist as to the information they provide about performance. This points up the need for information of this type. Unless a physician does something wrong enough to be the subject of an inquiry, he or she routinely receives little information on performance. Casual conversations are about the only way a physician has of comparing his or her performance with that of peers. Yet, materials do exist that can be used to provide information on patterns of practice. The Foundation for Health Care Evaluation and Blue Cross/Blue Shield are generating patterns of practice that cover such topics as hospital use, test use, and drug prescriptions in order to monitor quality of care. Because of the impact that improved information may have in shaping the individual physician's behavior, the Commission made the following recommendation:

RECOMMENDATION 7: FEEDBACK FOR PHYSICIANS

▪ The Foundation for Health Care Evaluation should include in the patterns of practice that are presently being generated criteria for cost-effectiveness as well as for quality. In addition, each practicing physician should be supplied with distributions of aggregate data and his or her own personal profile to compare with these distributions.

Modifying Reimbursement Structures for Hospital-Based Physicians

The last subject in the area of provider incentives that the Commission addressed was compensation of hospital-based physicians (laboratory pathologists, radiologists, anesthesiologists, etc.). While there is diversity in how these physicians are reimbursed and the kinds of contractual arrangements under which they work, two forms of payment are prevalent: the typical fee-for-service system and a system whereby reimbursement is based on the charges incurred within the department. While neither system is conducive to cost-consciousness, the latter system, partly because it is often used in the laboratory and radiology departments, can act as an incentive to disregard costs.

Primary providers generally order all procedures for their patients, but in the case of hospital-based specialties the complexity and sophistication of the procedures often causes the primary provider to rely solely on the specialists' recommendations. The Commission thought it inappropriate for hospital-based specialists to have positive incentives to disregard the costs of their orders; hence, the following recommendation:

RECOMMENDATION 8: HOSPITAL-BASED PHYSICIAN COMPENSATION

▪ Hospitals and their medical staffs should re-examine their compensation arrangements with contracted hospital-based physicians and devise compensation systems that encourage cost-sensitivity. Placing these contracted physicians on a fixed salary may be the first step in this direction.

CONSUMER INCENTIVES

Health-related behaviors are complex. Family systems, peer groups, education, temperament, and job constraints all influence diet, smoking, drinking, exercise patterns, stress management, and other factors that affect health. The variables that influence these behaviors are difficult to identify and almost impossible to control from a scientific point of view. As a consequence, the state of the art in intervention on health-related behaviors is primitive at best.

Almost any intervention program will show success when looked at in the short term, but almost no intervention program will show success when evaluated after a year or more. Put simply, we do not know how to make people change their health-related behavior and maintain these changes over the long term. Yet, when we look at such facts as these — women's average dress size has declined from 12 to 10 in the last 20 years, and the proportion of smokers in the middle-aged male population has declined from two-thirds to one-third — it is apparent that something is having an effect. What that something is and how it works is mysterious, however. As a consequence, the Commission was cautious in its approach to behavioral interventions, limiting its recommendations in this area to support of experimentation and pilot studies, and careful evaluation of the long-term effects. It seemed that the key incentives to try and enhance were the incentive for consumers to have and maintain personal health and the incentive for employers and third party payers to promote better consumer health in order to minimize expenses.

Promotion of Lifestyle Changes by Physicians

Physicians could have a far greater impact on patients lifestyles than they presently do. A study of several hundred Englishmen by Geoffrey Rose reported that nearly one-half of a study group stopped smoking after receiving only one examination by a physician and several sessions of physician counseling. Since the "quit rate" for almost any other intervention is approximately 25%, this study may indicate something about the potential that physicians have as health promoters. They are usually the only ones in a position to confront a person who is experiencing ill effects because of a given behavior, and due to the credibility that physicians usually have with their patients, this confrontation is likely to have significant impact.

Even though physicians *could* positively influence health-related behavior, they are too often reluctant to deal with it. Their training has not prepared them to deal with the complexities of behavioral intervention, and they are uncomfortable with it. Furthermore, it is unlikely that it will ever be cost-effective for a physician to do more than confront patients initially and then refer them to health behavior specialists for intervention. With these points in mind, the following recommendation was adopted:

RECOMMENDATIONS 9: HEALTH PROMOTION BY PHYSICIANS

- **Analysis of risk factors and lifestyle characteristics should be included in the routine physical exams given by every primary provider in the State of Minnesota. This analysis should include such determinations as:**
    - **☐ smoking habits**
    - **☐ physical activity level**
    - **☐ nutritional pattern**
    - **☐ chemical usage (alcohol, caffeine, drugs, etc.)**
    - **☐ weight, blood pressure, cholesterol levels, etc.**
- **Should a patient be determined to have risk factors, the physician should advise the patient to work on reduction of the risk factors and refer him or her to behavioral counselors within the physician's clinic or outside agencies specializing in such interventions.**

Implementation of this recommendation requires several things: First, a tool for analyzing health status that is sound from an epidemiological aspect and practical from an administrative point of view needs to be devised. Second, training for physicians and their staffs in terms of administration and interpretation needs to be developed. Third, people or agencies with competence in lifestyle intervention must be identified as resources for the physician community.

Health Promotion by Industry

Industry has much to gain if the health status of employees is improved. Lower health care premiums would be an expected result, along with reduced costs for absenteeism and reduced payments for disability. In addition, productivity may increase and profits may go up. On the basis of those potential payoffs for business, the Commission made the following recommendation:

RECOMMENDATION 10: HEALTH PROMOTION BY INDUSTRY

- **Major industry should actively experiment with health promotion programs in order to counteract the problems of absenteeism, excess numbers of sick days, and rising health insurance premiums. Some methods that should be considered are:**
    - **☐ development of in-house health promotion programs**
    - **☐ selection of reputable programs in the community and sharing of the fees for such programs with employees, providing that their attendance is good and that objective changes in risk factors last over sufficiently long periods to demonstrate that the changes are not temporary**
    - **☐ careful evaluation of the impact of these programs on morbidity, disability, absenteeism, productivity, etc.**
    - **☐ encouraging employees by means of incentives (for example, bonuses, earned days off) to participate in programs or "healthful" behavior patterns that demonstrate cost-effectiveness**

The business community is currently gaining interest in health promotion. However, much of the effort seems to be minimal, uncoordinated, and lacking in substance. It would seem logical at this point to pool efforts and conduct small-scale, reasonably controlled studies that will yield information about why programs may be effective and what degree of impact they can have so that business doesn't prematurely reach the point of saying, "We tried health promotion and it doesn't work." Perhaps a consortium of industry leaders, backed up by behavioral specialists and epidemiologists to design appropriate studies, would be the best approach.

Health Promotion by Third Party Payers

Third party payers could play an important role in promoting consumer health if they would reduce health or life insurance premiums for those practicing healthful lifestyles and if they would provide insurance coverage for lifestyle change programs. Both would provide clear financial incentives to the consumer to either persist in a healthful lifestyle or change to such a pattern.

Unfortunately, translating behavior patterns into insurance premiums is not easy: On what actuarial basis does one determine the risk factors and the associated rates for lifestyle characteristics? Although data from Lester Breslow's studies[4] indicate that the "seven golden rules of good health" (eat breakfast, get seven hours of sleep, don't smoke, etc.) are predictive of reduced morbidity and increased longevity, and the data from the Framingham Study[5] does the same for cardiovascular risk factors, these data are not adequate for establishing rates.

Assuming it became possible to determine rates for lifestyle risk factors as well as for the "harder" data such as blood pressure, obesity, and cholesterol level, the problems then would arise of guarding confidentiality, verifying data, and updating data. Smokers, drinkers, and the overweight are notorious for under-reporting their key behaviors. If clinical measures such as thiocyanate and serum cholesterol levels were to be used as evidence of change, then other complex questions arise: How is baseline determined? Who pays for all these measures? How are the laboratories standardized?

Last is the problem of how to treat high-risk families or individuals for insurance purposes. Some form of pooling of these individuals would no doubt have to be done if a risk-factor approach to rating insurance were to be implemented on a broad scale. In spite of these serious considerations, the Commission felt that the area should be explored:

RECOMMENDATION 11: HEALTH PROMOTION BY THIRD PARTY PAYERS

- **Health insurance carriers should conduct pilot studies on tying premium charges to risk factors and lifestyle characteristics such as smoking patterns and level of physical activity. Particular attention should be paid to those risk factors under the control of the individual. Furthermore, third party payers should review intervention programs and identify their cost-effectiveness. Should the programs be determined to be cost-effective, third party payers should consider extending coverage to them.**

This recommendation raises the entire issue of the expanding boundaries of health care. The original concept of health care and the insurance that went with it was based on the *medical model*: disease, treatment, and reimbursement for that treatment. Today, emphasis is shifting to a *health model:* fitness, mental equanimity, and satisfactory interpersonal relations, for just a few of its components. Health is now defined "holistically" to include the entire person, not just his or her physical ills. A central issue will eventually have to be faced as we move in this direction: How much pursuit of total health should society underwrite in the form of reimbursement and how much should the individual underwrite? Presumably, the choice of how healthy one desires to be is reflected in one's values and commitments to healthful habits and lifestyles. Should the committed individual be reimbursed for his or her commitment at the expense of the uncommitted? And conversely, should the committed have to bear the financial burden of the consequences brought about by the lifestyles of the uncommitted?

INSTITUTIONAL INCENTIVES

The recommendations that follow approach institutional incentives through four basic avenues: reducing the incentive to overtreat, reducing utilization of high-cost acute-care facilities through encouragement of alternative treatment modes, modifying rates and charges in order to make hospitals account more precisely for their activities and charge more appropriately, and encouraging reduction of excess capacity.

Reducing the Incentive to Overtreat

As already stated in the discussion of provider incentives, the Commission felt that inappropriate utilization should not be reimbursed by third party payers or by consumers but that a provider or an institution should be at risk for whatever inappropriate care is rendered. Once a patient has arrived at an institution, the possibility of eliminating a problem before it occurs is either reduced or impossible. At that point, the next best approach is to monitor the care delivered to make sure it does not extend longer than necessary, as suggested in the following recommendation:

RECOMMENDATION 12: LENGTH OF STAY

- **Hospitals should perform concurrent utilization review and quality assurance review (retrospective quality audits) for a sample of patients regardless of payment source.**
- **During concurrent review, should the care already rendered be found to be obviously inappropriate, the hospital and the attending physician should be at risk. If the provider indicates to the patient that additional hospital care is not medically indicated, the patient should be advised that any additional care will have to be paid for at his or her expense. Should retrospective review reveal a repeated pattern of overutilization, a program of sanctions should be implemented in the institution involved.**

The process employed by the Foundation for Health Care Evaluation to accomplish concurrent review is already widespread throughout the State of Minnesota. Financing details can be worked out using the existing programs as models. North Central Health Protection Plan, administered by the Employers of Wausau insurance company in Wausau, Wisconsin, is an example of a successful model: in this plan, "repeat offenders" of unnecessarily long hospitalizations are subjected to a series of sanctions of increasing severity.

The Commission felt that another cause for concern in regard to institution incentives was the "race" to provide more and more elaborate services. The incentive that hospitals have to provide the best services possible for their staff physicians, combined with the incentives of the other health professionals (nurses, inhalation therapists, rehabilitation specialists, etc.) to establish their professionalism and improve the quality of their care, has led to an overelaboration of services performed. This chain of events has accelerated the cost of care, since instead of one charge for nursing services, for example, additional charges are now made for the specialty services performed by a variety of health care professionals. These services are not without merit, but have expanded to the point where they should be carefully evaluated for cost-effectiveness. Therefore, the Commission made the following recommendation, which they broadened to include a wide range of therapeutic procedures rather than only those in which a specific professional is involved:

RECOMMENDATION 13: TREATMENT MODALITIES

- **The medical specialty societies in Minnesota should define acceptable treatment modalities and conduct controlled studies with clearly defined protocols to determine the costs and benefits of these various modalities, including the alternative of no treatment whatsoever. Such factors as quality of life and improvement in productivity should be measured along with morbidity and cost in the studies.**
- **Reimbursement for existing treatment modalities should continue only if the professionals involved are willing to participate in such studies. Furthermore, all new treatment modalities should go through such an evaluation process prior to reimbursement by third party payers, and no new clinical treatment should be approved for reimbursement without its cost-effectiveness demonstrated. In cases of dispute regarding reimbursement, the third party payers could turn to the specialty societies for judgment.**

In addition to examining existing therapeutic procedures, the Commission felt that even clinical research should be concerned with cost-effectiveness, as indicated by this recommendation:

RECOMMENDATION 14: CLINICAL PRACTICES

- **Agencies and federal, state, and private foundations which fund studies of clinical practices should require cost-benefit analyses and rigorous outcome evaluations in grant work.**

In order to implement both of the previous recommendations, some common "language" needs to be developed so that studies being conducted can be compared with each other. Many of the things being measured in cost-effectiveness evaluations — life, happiness, productivity, etc. — are complex and problematic to measure, so arbitrary measures will be necessary. It is important, however, that these arbitrary measures be consistent. Otherwise it is impossible to make cross-comparisons between treatments and studies. Perhaps a task force comprised of representatives of the specialty societies, experienced epidemiologists, and behavioral scientists could be assembled to work on this task.

Reducing Utilization of Acute-Care Facilities

Graduated Levels of Care. The argument for reducing utilization of acute-care facilities is a simple one, at least on the surface: If one does not have to incur a hospital charge, then it makes good economic sense not to do so, because acute-care hospital services are a very expensive way of delivering care. In viewing a typical hospital with an eye trained to pick out patients whose conditions do not necessarily require the high-cost services of an acute-care facility, many examples might be noted:

— ambulatory patients quite capable of taking care of their personal needs

— patients hospitalized simply for diagnostic tests

— patients hospitalized only because there is no one to take care of them at home.

— patients admitted for very simple procedures not requiring the elaborate technology available

— terminal patients requiring personal attention and services but not at a high level of medical care

All of these categories of patients would probably be discovered in any acute-care hospital and the charges for all would be approximately the same despite the graduated levels of care involved in each and the lack of actual acute-care requirements in all.

A reasonable goal would be high quality care rendered in the most cost-effective setting. Consequently, patients should receive the level of care they need and no more. Various proposals and experiments are underway to address the problem of delivering good care in the most minimal setting. Among them are the Minnesota Medical Association's Ad Hoc Committee on Cost Containment, whose primary focus has been on transferring procedures normally done in hospitals to physicians' offices, and various experiments being conducted by third party payers on reimbursing home care, care in hospices, and care in freestanding ambulatory surgical centers.

The most obvious solution would appear to be reimbursing patients for care received in the less expensive facilities, but there are some major problems with this "simple" approach: If even less of the now-existing hospital capacity is used, hospital charges will go *up* to cover losses — at least temporarily (presumably, the weakest hospitals would eventually fold). Second, if reimbursement extends to all of the seemingly more cost-effective possibilities — transferred procedures, surgicenters, hospices, extended care facilities, and others — have we not simply fueled demand by adding coverage? If so, consumers would end up paying for acute care *plus* the added types of care, and costs in the health care system would rise even more. Third, there is the practical problem of accounting systems in hospitals. If hospitals can convert beds from one level of service to another, how does the accounting system determine what a "bed" is — today it may be an acute-care bed, tomorrow a skilled nursing bed. The only solution might be to designate whole floors or wings to specified levels of care.

A potential solution to the first problem — redistributed costs — would be to reduce or utilize efficiently the excess capacity in the system (this will be dealt with in more detail later in the report). The second problem — fueling demand by extending coverage — might be dealt with by designing coverage so that added services are covered only if they are *substituted* for acute-care hospital services. Other possibilities undoubtedly also exist for addressing the problems that may arise.

RECOMMENDATION 15: GRADUATED LEVELS OF CARE

▪ **Third party payers should promote development of adequate insurance coverage for high quality care rendered in the most cost-effective setting. Among the types of services to which coverage should be extended — provided that they are demonstrated to produce a net reduction in services rendered, thus reducing the cost of health care to the community as a whole — are:**

- ☐ **health services delivered out of a hospital setting**
- ☐ **skilled intermediate services and facilities**
- ☐ **home health care**
- ☐ **ambulatory care**
- ☐ **hospices**
- ☐ **community services provided by hospitals**

Evaluation of the cost-effectiveness of such extension of coverage would be a necessary part of implementing this recommendation on a broad scale, as well as continued surveillance after implementation.

Preadmission Testing. Another strategy for reducing utilization of acute-care facilities is the encouragement of preadmission testing programs. In these programs, coverage is extended to include lab work and x-rays done on an outpatient basis prior to hospital admission. Possible misuse of preadmission testing is frequently avoided by enforcing the following requirements:[6]

— *Diagnostic tests other than those confirming the admitting diagnosis will not be covered*

— *Testing is covered for a limited time prior to a scheduled admission*

— *Testing must be ordered by the attending physician*

— *A forthcoming admission must be confirmed before testing takes place*

Data regarding the efficiency of the program are conflicting to date. Theoretically, this type of testing should reduce the total number of days spent in the hospital by one or two per surgical admission. Yet, in fact, for the programs to work as expected, several conditions appear necessary:[7]

— *Tests done outside the hospital must meet the quality standards of the admitting hospital*

— *Test or x-ray results must be accepted by the hospital*

— *The transmission of data from the physician's office to the admission office and the other hospital departments must be well coordinated*

— *The procedure must be accepted in both the provider and hospital community*

— *Training must be available for the personnel involved*

Keeping these requirements in mind, the Commission adopted the following recommendation:

RECOMMENDATION 16: PREADMISSION TESTING

▪ **Third party payers should encourage preadmission testing on an outpatient basis in order to reduce hospital utilization. These tests should be of high quality and performed in the most appropriate setting. Reimbursement should be made on the most favorable basis under the contract, which may mean modifying or waiving both the deductible and the coinsurance clause.**

Reducing Emergency Room Utilization. Emergency rooms are now used far in excess of what is necessary. Some of the reasons behind this overuse are:

- Many consumers have no primary provider so use the emergency room as their personal "doctor."
- It is more convenient for the consumer to use the emergency room during lunch hours and immediately after work.
- It is often more convenient for a physician's office to send a patient to the emergency room than to crowd a full schedule or schedule a patient after hours.
- Some procedures not covered in a physician's office *are* covered by insurance in an emergency room.
- Consumers have little idea of when it is appropriate to use the emergency room.
- Hospitals encourage emergency room use because the emergency room is a way of collecting more patients and hence, more income.

This overutilization of emergency rooms generates excess costs. For one thing, an emergency room visit typically costs upwards of $60, while an office visit ranges from $12 to $20. Also, emergency room physicians usually have no medical history when they treat a patient, so must perform extra testing and diagnostic procedures. Then, there is the additional incentive to use hospital facilities, whether absolutely necessary or not, because of their availability. The possible resulting overtreatment is not best for the patient, and demonstrates the fact that one should be concerned not only with the actual costs of emergency room overutilization, but also with other "costs" — such as potential compromises in quality of care.

The fact that emergency room use peaks during the lunch hour and between the hours of 5 and 7 p.m. indicates that much of the facilities' usage is probably not related to medical emergency. By using a telephone screening service, one local clinic, Community University Health Care Center, has reduced the percentage of emergency room visits considered neither urgent nor serious to less than 10%. This is significant in comparison with the fact that 41.49% of emergency room visits in the overall metropolitan area are of this type, and indicates that much could be done to reduce excessive emergency room use. On the basis of this, the Commission adopted the recommendation below:

RECOMMENDATION 17: EMERGENCY ROOM UTILIZATION

- **Physicians should explore ways to reduce emergency room usage by their patients by considering such policies as:**
  - **"lunch hour" coverage in physicians' offices to avoid unreferred emergency room visits**
  - **shared telephone screening systems with other physicians within a practice or with other practices in the area**
  - **lengthened office hours on a rotating basis in either physicians' offices or clinics and, if necessary, appropriate arrangements with other offices that are geographically proximate, to lengthen the "business day"**
- **Third party payers should penalize indiscriminate use of the emergency room by:**
  - **adding appropriate copayments or deductibles to emergency room use**
  - **eliminating favorable treatment (reimbursement) of procedures done in the emergency room instead of in a physician's office**
- **Physicians in the emergency room should:**
  - **conduct no investigative work without first contacting the patient's physician, except in cases of real emergency**
  - **advise the patient to get a primary care physician if he or she does not have one**
- **Consumers should be furnished with a self-diagnostic handbook that advises them when to call a physician and what to tell him or her, and when to go to the emergency room.**
- **Last, a public campaign should be undertaken to inform consumers of the excessive costs of emergency room use and of the benefits both in cost and in quality of care attainable through having a primary provider.**

Because of the high costs of operating emergency rooms, the Commission wished to encourage hospitals to look carefully at how costs could be reduced in this area. Therefore, the recommendation below was adopted:

RECOMMENDATION 18: EMERGENCY ROOM PRACTICES

- **Every hospital having an emergency room should review both its staffing patterns and its modes of practice, and institute whatever changes may be indicated to increase cost-effectiveness.**

If utilization of acute-care facilities is reduced by the methods discussed — promotion of graduated levels of care, encouragement of preadmission testing, and reducing emergency room usage — occupancy rates in these facilities will be substantially lowered. Once occupancy rates drop below a certain point, hospitals will be forced to reduce capacity in some manner: the possibilities include closure or conversion of facilities, consolidation with other hospitals, and sharing of services. The major incentive operating will be achievement of economic survival rather than expansion of services.

Reducing Hospital Capacity

The short-term effects of closing entire hospitals or even hospital wings are economically painful to local communities, so efforts to reduce capacity should be undertaken carefully. The issues involved are complex, as indicated in the following recommendation:

RECOMMENDATION 19: HOSPITAL CAPACITY REDUCTIONS

- **Recommended reductions in hospital capacity in a community should be based on a generally accepted policy framework; careful measurement of community needs; a cost-effective priority system; a plan for resolving such issues as resulting unemployment, debt payment, and retention of health care professionals within the community; and, finally, a proposal that has been agreed upon by key parties in the community health care system for an orderly process of carrying out the overall strategy.**

A recent report entitled "Recommended Changes in the West Metropolitan Health Care System: The Voluntary Sector's Approach," prepared by the West Metro Hospital Trustees' Council in Minneapolis, is a good example of a well-planned process for arriving at appropriate recommendations for reducing hospital capacity.

Planning for capacity reductions in the *rural* hospitals of Minnesota is a particularily difficult and complex task. These hospitals have far lower occupancy rates than metropolican hospitals, but, paradoxically, closing the facilities may achieve very little economic advantage. According to **Table 3**, we could shut down 67 hospitals, nearly half of the 151 in the state, and still save only 5% of the total hospital expenditure in the state.

Table 3. Minnesota hospitals ranked by budget share

Number of hospitals ranked by size of 1977-78 budget	Proportion of total sector budget (%)	Portion of total number of hospitals* (%)
Top 8 hospitals	40	5.3
Top 12	50	7.9
Top 17	60	11.3
Top 28	75	18.5
Top 44	85	29.1
Top 58	90	38.4
Top 84	95	55.6

**Total numbers of hospitals = 151*

Source: Dahl, Tor: Containment of Health Care Costs – The Case of Minnesota. A report to the Health Care Cost Commission of the Minnesota State Medical Association; Dec. 13, 1977. p. 53.

Another consideration in regard to rural hospitals is that the rate of increase in their budgets is proportionately lower than the rates in the bigger hospitals. By closing these hospitals, we would in effect be shifting patients from low-cost to high-cost facilities.[8] Apparently, a bed-to-population ratio is appropriate to use as a *guideline* but cannot be used as an *absolute* when examining local conditions. Also it is quite evident that closing rural hospitals may not accomplish much in reducing costs. Because the Commission felt that caution should be exercised in planning reductions in these settings, it adopted the recommendation below:

RECOMMENDATION 20: REDUCING CAPACITY IN RURAL AREAS

▪ A study focusing on the hospitals outside the seven county metropolitan area should be undertaken by the State Health Planning and Development Agency. This study should evaluate the social, economic, professional, and legal implications of:

- ☐ **closing entire hospitals**
- ☐ **sharing services between hospitals**
- ☐ **closing services within a single hospital**

The following recommendation was adopted out of the Commission's concern that undue hardship might result from closing hospitals:

RECOMMENDATION 21: FINANCIAL COMPENSATION FOR CLOSURE

▪ If publicly mandated closure forces a hospital to close on the basis of excess capacity alone and it is demonstrated that the bondholders or other creditors will suffer economic loss despite sale of land or building, then public funds should be made available from the state and/or federal government to provide relief.

Despite the notes of caution brought out by the Commission regarding the reduction of hospital capacity, the Commission did clearly support such reduction with the opinion that only when excess capacity is eliminated will there be any chance of stabilizing costs in the health care field.

Modifying Rate Structures, Reimbursement Mechanisms, and Management Efficiency

Rate Structures. Hospitals offer a smorgasbord of services with a wide range of personnel and technology associated with each service, yet patients receive a uniform charge for a bed regardless of how representative this charge is of the costs and services in a given department. The rationale behind this is the simplification it allows in the hospital's accounting and billing processes. Along with the simplicity it achieves, however, it also conceals a great deal: First of all, it makes it impossible to know how charges were arrived at. Furthermore, it is impossible to compare one hospital's charges with another's because the charge represents aggregate data. Last, patients in low-cost hospital departments are subsidizing those in high-cost departments — the former patients are in effect being overcharged, while the latter are being undercharged.

In general, the Commission thought that patients should pay for the complete cost of services *they* receive but *not* the costs associated with services rendered to *other* patients. Services now incapable of producing enough revenue to meet costs should generate the needed revenue through either increased charges or decreased costs. The savings resulting from not subsidizing revenue-losing departments should be passed on to the patient in the form of lower costs.

RECOMMENDATION 22: REVISING HOSPITAL RATE STRUCTURES

▪ The hospital rate structure for acute-care services should be modified so that revenue produced by specific services covers the cost of providing those services, thereby preventing — insofar as possible — the subsidizing of services not producing enough revenue to meet their costs.

It should be made clear that this recommendation refers primarily to acute-care services in urban areas. Much controversy arises over non-acute-care services that hospitals provide and over the issue of what services should be offered in rural hospitals and at what price. In general, the Commission felt that services should not be performed in acute-care hospitals unless the costs — both fixed and variable — are less than they would be in other settings. In regard to rural hospitals in particular, the Commission felt that the provision of non-acute services could be cost-effective if the costs of those services covered all of their variable costs and made some contribution toward their fixed costs. This would ensure that acute-care charges would not subsidize non-acute-care services.

Implicit in successful revision of rate structures is the need for hospitals — at least major hospitals — to agree to report uniform data so that costs can be identified across hospitals and cost centers can be compared with each other. Presumably, cost-consciousness might be raised and competition enhanced if it were clear what rates reflected.

Medicare/Medicaid Charges. Medicare and Medicaid cost formulas do not reimburse hospitals for their legitimate financial requirements as defined by the Minnesota Rate Review Regulations. This fact has greatly escalated costs to non-Medicare/Medicaid patients (about one-half to two-thirds of all patients are private paying patients): Metropolitan hospitals have estimated that rates could be lowered $15.00 to $20.00 per day to all non-Medicare/Medicaid patients if those programs were to reimburse on the basis of the Minnesota Rate Review Program.

The same principle that applied to hospital charges in the previous section applies here: No service — or in this case, no patient — should be subsidized at the expense of another. In the case of Medicare and Medicaid patients being subsidized by private-paying patients, the situation is perhaps more striking even than the previous case of acute-care patients being subsidized by non-acute-care patients because it is the sick in our society who are subsidizing the government in the former situation. In view of this, the Commission adopted this recommendation:

RECOMMENDATION 23: MEDICARE/ MEDICAID REIMBURSEMENT

- **Medicare and Medicaid should reimburse institutions on a basis that discourages subsidy by private-paying patients.**

Hospital Management. Hospitals are enormously complex operations. Minnesota's hospitals have done some outstanding work in implementing new and sophisticated management techniques: A centralized staffing system at Methodist Hospital in St. Louis Park recently reported a $220,000 savings in nursing salaries based on a sophisticated management engineering study, and St. Mary's Hospital has developed a staffing allocation system that responds almost immediately to patient-care requirements.[9] The Commission commends these successful management efforts and encourages other institutions to follow the example. The following recommendation was made in view of the fact that good information is the basis of good management but that delivering care is a rapidly changing art that is difficult to keep up with.

RECOMMENDATION 24: AN INFORMATION CLEARINGHOUSE

- **An information clearinghouse should be established that identifies and locates literature on the latest strategies and techniques in the area of hospital administration, and literature reviews on selected subjects should be available upon request.**
- **Hospitals should use these services and adopt promising techniques as they are identified.**

Possible sponsoring agencies for the proposed clearinghouse include the Minnesota Hospital Association and the Council of Community Hospitals in the Twin Cities.

The Board of Directors. A ready source of support and relevant expertise for cost-accounting and the application of management techniques to cost-containment is a hospital's Board of Directors, usually made up of well-respected and highly competent members of the local business community. Until recently, the role of these persons was to act as a sounding board rather than to provide active leadership. Currently, however, board members have become far more active. Because the Commission felt that these individuals could potentially offer valuable help in the direction of efficiency and cost containment, the Commission wished to encourage their increased involvement by adopting the following recommendation:

RECOMMENDATION 25: HOSPITAL BOARDS

- **Members of the Board of Directors of hospitals should become even more active in promoting strategies for cost containment in the hospitals. They should make increasing demands on administrators for well-thought-out plans for cost analyses, efficient staff allocations, and means of reducing capacity such as merging, consolidations, and sharing services with other hospitals.**

By adopting incentives to provide services carefully, to account rigorously, to manage efficiently, and to reduce excess capacity, as outlined in the foregoing recommendations, hospitals may be rewarded by controlled or even reduced costs, in their own facilities and in the overall health care sector.

THIRD PARTY PAYER INCENTIVES

The single recommendation adopted by the Commission that will affect the incentives of third party payers (here referring primarily to insurance carriers) is Recommendation 2 — that employers offer multiple choices among conventional insurance plans and health care plans. This policy would have the effect of forcing insurance carriers to compete with health care plans for enrollees, and ultimately for survival: Were insurance carriers unable to compete effectively in terms of price and service, they would not survive. In the competitive climate, the carriers would necessarily have to become more conscious of controlling expense ratios in claims processing and more conscious of utilization patterns that drive up costs and thus premiums. As a result, third party payers would have an incentive to initiate programs aimed at reducing indiscriminant utilization — be they preadmission screening, concurrent review, retrospective audit, or consumer education in self-care and efficient use of the health care delivery system.

Another tack that carriers would no doubt undertake in the midst of competition would be the formation of their own health care plans. Blue Cross/Blue Shield has already done this in Minnesota. It is a logical course of action for carriers since they have so much valuable actuarial and administrative expertise and such considerable skill and experience in marketing. Apart from their potential role in organizing and developing health care plans, another service they might offer would be administrative services to health care plans. Clearly, with the advent of multiple health care plans, insurance carriers have new and special markets open to them.

All of the Commission's recommendations that directly affect the incentives of the provider, consumer, institution, or third party payer have now been presented. Next are the recommendations that deal with teaching consumers and providers about cost-sensitive and cost-effective behavior.

Chapter 5

Recommendations Aiming at Cost-Effective Behavior

The recommendations in Chapters 3 and 4 imply the necessity for the provider to "provide" and the consumer to "consume" health care services in a more cost-effective manner. This would be easy enough if all providers and consumers knew what cost-effective behaviors were, but this is not necessarily the case. Providers have traditionally focused only on the quality of care, and consumers have generally been concerned with obtaining more benefits and wider coverage — neither group has been particularly interested in cost-effectiveness. The reasons for the lack of interest are many. The incentives operating in the system — as discussed earlier — have provided no reason to be concerned with cost on the part of either provider or consumer.

RAISING COST-SENSITIVITY IN THE PROVIDER

The management of medical problems lends itself to a wide variety of alternative choices, the outcomes of which have not been evaluated for cost-effectiveness. In short, medicine as it is currently practiced generally aims at effectiveness but not cost-effectiveness. Evaluating the latter is fraught with difficulties: Comparative evaluations of alternative medical procedures lack the glamour or interest surrounding the pioneering of a new diagnostic or treatment procedure. Furthermore, these evaluation studies are notoriously difficult to conduct. "Health" and "well-being" are difficult to measure in comparison with clinical end-points. Identifying the costs that should be included and developing measurement instruments are complex processes requiring skills other than those traditionally taught to physicians. Because of these difficulties, there have been few rigorous outcome studies measuring cost-effectiveness, and there are few procedures that can truly be claimed as "cost-effective."

It is clear that raising cost-sensitivity in providers is a complex task involving subject matter new to many physicians. The first step toward making this "foreign" concern of cost a normal part of every physician's decisionmaking process is to define the standards against which behavior can be measured to determine whether or not it is cost-effective.

Developing Criteria for Desirable Practice Patterns

The central thesis of Recommendations 26 through 32 is that certain patterns of practice are identifiable that are recognizably more cost-effective than others. Once identified, these patterns can be taught and knowledge of these patterns can be tested for. They do *not,* as stressed by the Commission, refer to *norms of practice* or *protocols,* for norms refer to the customary and usual, the accepted and traditional, the codification and structuring of a process. These are *not* characteristics that are part of the criteria for identifying cost-effective patterns of practice. Rather, the criteria referred to here can be thought of as the medical analogs of the economist's productivity measures or of the industrial engineer's efficiency measures: They represent equations — not process; interrelationships and mathematical functions — not steps in a prescribed sequence of events. Put simply, they are not meant to suggest "cookbook" medicine in any sense.

RECOMMENDATION 26: DESIRABLE PRACTICE PATTERNS

- **Criteria for desirable patterns of cost-effective practice should be developed for broad disease categories. Once developed, the criteria should be published in the professional journals to increase their dissemination and utilization.**

There are a variety of groups in the state into whose domain the activity suggested in this recommendation might fall — the specialty societies of the Minnesota Medical Association, the medical schools, various health care research organizations, and others. A consortium of interested parties may be the best way to approach the task. The National Center for Health Services Research is willing to fund small grants of $35,000 or less for research in the area of cost containment, an area into which this activity would certainly fall.

Making the Criteria Widely Understood and Practiced

Once criteria have been established for patterns of practice that are cost-effective and hence desirable, they must be widely disseminated and taught so that cost will become a normal consideration in every physician's daily decisions. The "message" can be spread in many ways that fall into two categories — educating the physician-in-training and re-educating the practicing physician.

Educating the Physician-in-Training. If cost-effective patterns of practice were widely taught to medical students and residents, not only would they be routinely exposed to some of the important criteria by which future performance would be judged, but also their attitudes and behaviors would be well shaped by the time they began practicing. Several routes can be used to reach the physician-in-training.

Include the criteria in medical school curricula. It is the Commission's hope that the criteria of cost-effectiveness be included in *all medical school courses* that deal with diagnostics and therapies for specific diseases. Dispersing the criteria *throughout the curriculum* would also avoid a potential problem brought on by a single course in medical economics or cost-effective medical practice — namely, a student's dismissal of the course's content because of its apparent isolation from the rest of his or her courses. Dispersing the criteria would also present a positive challenge to faculty because of the subject matter's newness both to them and to students. Because the Commission believed that this approach had great potential for changing the current style of medical practice to a more cost-effective one, the following recommendation was adopted:

RECOMMENDATION 27: MEDICAL SCHOOL CURRICULA

- **Once the criteria for desirable practice patterns for various disease categories are developed, they should be incorporated in the proper courses in medical school curricula. Criteria should be developed first for inclusion in the basic clinical courses required of most medical students.**

In order to implement this recommendation, the consortium or other group charged with developing the criteria should identify "high visibility" medical school courses where the introduction of these criteria would have the greatest impact. School curriculum committees must be heavily involved in this process. The gradual introduction of "new" subject matter on a course-by-course basis should make its acceptance and adoption easier.

Incorporate the criteria in clinical reviews and case presentations. Just as clinical findings are a normal consideration in every physician's decisions, so should be the established criteria of the cost-effectiveness of different practice patterns. One way of encouraging the latter to become an integral part of decisionmaking is to insure that the criteria *permeate* the activities to which medical students and residents are exposed. Actual practice in using the criteria will be much more effective in shaping students' thinking and behavior than simply listening or reading about them. Therefore, the Commission adopted this recommendation:

RECOMMENDATION 28: CLINICAL REVIEWS AND CASE PRESENTATIONS

- **As the criteria for cost-effective patterns of practice are developed, they should be incorporated in clinical reviews. Evaluation of case presentations should include consideration of these criteria as well, and they should take their place alongside clinical indications in discussions of adequacy of care rendered.**

One way of implementing this recommendation would be to use medical students and first year residents to assist in auditing the application of the cost-effectiveness criteria to actual cases and reviews. In this way, students and residents would gain practice and facility, and those presenting cases or reviews would have some support and assistance. Early efforts in this direction have been undertaken by each of Minnesota's three medical schools, for which they are commended by the Commission.

Test for cost-sensitivity. When a person's performance in a given area is being monitored and evaluated, it is likely that his or her behavior in that area will be positively affected. Consequently, if medical students' cost-sensitivity were measured and given a value along with their knowledge in other subject areas, they would probably develop and practice more cost-effective behavior. Since physicians generally develop their style of practice during residency, it is particularly important to reward cost-effective behavior at this time.

Before a resident sits for the board examination, his or her performance is evaluated by the medical department's staff to ensure his or her readiness to take the examination. It would seem reasonable to include demonstrated cost-sensitivity of a resident among the criteria for readiness; established criteria for cost-effective practice patterns could be used in part to make this determination. It would also be desirable to include cost-sensitivity among the areas actually tested for. The clinical management sections of some boards are already doing this. The Commission commended those actions and made the following recommendation:

RECOMMENDATION 29: BOARD EXAMINATIONS

- **Where testing for cost-sensitivity is not already included in the clinical management portion of**

board examinations, the specialty boards of the Licensing Committee of Graduate Medical Education who accredit residency programs should develop such testing mechanisms. Furthermore, inefficient and redundant choices of procedures should be heavily penalized in the scoring of such exams.

The Commission suggested that the most effective method of implementing this action might be for the Minnesota Medical Association in conjunction with the various specialty societies to carry the recommendation to the particular boards. It would also be within the charge of the Minnesota Medical Association to follow up on this recommendation to determine what actions were being taken.

Re-educating Practicing Physicians. Recommendations have now been made that can affect positively the physician-in-training, but the practicing physician must not be ignored, for it is this physician who is responsible for the bulk of the decisions affecting costs in the health care field. There are several avenues for encouraging cost-sensitivity in the practicing physician: Two natural ones are through public concern and through the example of peers' modes of practice. Public concern is already high, as evidenced by the very existence of this Commission, for one example. The large number of newspaper and magazine articles being written about health care costs have made it an issue of high visibility. As more and more physicians become sensitized to cost issues, changes they make in their style of practice will begin to be noticed by their colleagues and will affect those colleagues' styles of practice: a "ripple" effect will likely take place. The Commission identified several other avenues through which practicing physicians might be re-educated as well.

Accredit Continuing Medical Education courses. Because the Commission members believed that the practicing physician should be exposed to the same criteria for cost-effective patterns of practice as the physician-in-training, this recommendation was adopted:

RECOMMENDATION 30: CONTINUING MEDICAL EDUCATION

- **As the criteria for cost-effective patterns of practice are established, they should become an integral and substantial part of Continuing Medical Education programs. In specific Continuing Medical Education courses, physicians should be required to consider the costs implicit in the procedures under discussion.**

In order to implement this recommendation, those bodies in the state that are responsible for accreditation of Continuing Medical Education courses should devise a plan of action for incorporating the "new" subject matter and coordinate their efforts with groups responsible for devising criteria for cost-effective patterns of practice.

Evaluate cost-sensitivity in audits of quality. Physician testimony before the Commission made it clear that physicians are frequently unaware of the costs of tests and equipment, as well as of duplicated effort. In an attempt to remedy this situation, the Commission adopted the following recommendation:

RECOMMENDATION 31: COST - EFFECTIVENESS IN AUDITS

- **As the criteria for cost-effective patterns of practice are developed, they should be included routinely in audits of medical quality.**

Hopefully, physicians would become sensitized to their own practice patterns as feedback on performance became routine. With medical students and residents assisting in the audits, it should be possible to implement the recommendation in a way that is not onerous to anyone.

Encourage cost-effective utilization of laboratory and radiology procedures. The Commission felt that laboratory and radiology use should have early priority as a target for cost containment, first because there is a great need for more cost-effective performance in these areas, and second because effecting changes in them will be compartively easy due to the straightforward nature of the subject matter — it demands nothing as complex as developing "criteria for cost-effective practices," for example. Furthermore, laboratory and radiology use is an area where small changes have the potential for yielding great savings.

The current overuse or inefficient use of laboratory tests and radiology procedures arises both from the incentives operating in the system and from the complexity of and rapid technologic advances taking place in the two fields. The incentives now operating to encourage sometimes indiscriminate use of such procedures as lab tests and radiology have been considered already. As for the second point, both laboratory and radiology departments are centers for high technology and the exploration of new techniques and new tests. The advances in sophistication and complexity are astounding when present tests and procedures are compared with those available 20 or 30 years ago. These advances have brought with them the facts that tests and procedures become outdated very quickly and that, with the wide range of choices available, the decision to choose between one method and another becomes very complex. The Commission thought that much could be done to educate physicians in the appropriate selection of tests and procedures, so adopted the recommendation below:

RECOMMENDATION 32: LABORATORY AND RADIOLOGY USE

- **A guide should be developed to aid physicians in making cost-effective choices regarding laboratory procedures in the context of an entire episode**

of care. This guide should contain information about the specificity, sensitivity, approximate price, and any other useful information that might aid the physician in deciding whether to use a procedure or which of two or more procedures to use.

- **A similar guide containing analogous information should be developed for radiology procedures.**

One approach to implementing this recommendation would be to first define the areas in which physicians need the most guidance. Direction might be taken from the Jackson Memorial Hospital in Miami, Florida, where medical students, faculty, and staff were tested as to their knowledge of the charges for various tests. The process served to sensitize all parties regarding their level of cost knowledge and allowed them to pinpoint areas of least knowledge. Were problem areas to be identified through such means, the guides recommended above could be focused upon them and perhaps Continuing Medical Education programs could include instruction in them.

Encourage cost-sensitivity in other hospital areas. The Commission's discussion of cost-sensitivity in the areas of laboratory and radiology procedures raised the question of cost-sensitivity in other hospital departments and procedures. The general feeling among the members was that much could be done to sensitize the physician to the costs of his or her actions throughout the hospital, and led to this recommendation:

RECOMMENDATION 33: COST-SENSITIZING

- **Hospital administrators and their medical personnel should devise plans to sensitize their staffs to the costs of procedures typically performed in each department. This "sensitizing" process should occur frequently enough so that physicians and other staff are kept current on costs.**

Among the potential vehicles for accomplishing this recommendation are periodic staff meetings, selective case reviews, medical audits, and price posting.

All of the recommendations regarding sensitizing the provider to cost are, in the Commission's opinion, of utmost importance. By making providers become accustomed to thinking in terms of cost-effectiveness in medical practice, *the groundwork is laid for the day when physicians will be held financially as well as clinically accountable in the management of their patients.*

RECOMMENDATION 34: HEALTH PROMOTION TASK FORCE

- **The Health Care Coalition* should establish a *temporary* Health Promotion Task Force charged with two main responsibilities:**
  - **☐ to identify how a health promotion strategy may best be developed and implemented through the state**
  - **☐ to evaluate the cost-effectiveness of intervention programs that already exist and design an evaluation system to uniformly monitor the cost-effectiveness of new intervention programs across the state.**

Both of the responsibilities outlined in this recommendation deal with public policy at the broadest level, so should be addressed using a broad range of expertise and interests. One major impediment to developing public policy in this particular area is the current lack of baseline data on health status, risk factors, and lifestyle characteristics of the Minnesota population. This lack makes it difficult to identify and investigate problem areas, to evaluate the effectiveness of any intervention programs undertaken, and to determine an appropriate direction for public policy in the area. Therefore, the Commission felt that the State Health Department or some other institution with demonstrated epidemiological expertise should develop a reporting system that collects this data routinely. However, rather than reempt the prerogatives of the Task Force on Health Promotion, the Commission felt that it would go on further in preparing a recommendation and specifying action in this area.

Improving Health Education in the Public Schools

If children were taught to adopt good nutritional patterns, to establish exercise as a consistent part of their lives, to moderate or avoid the use of chemicals (alcohol, tobacco, and other drugs), and to practice good hygiene, an enormous reduction in morbidity and health care costs would be a likely consequence. Increased well-being would pay dividends of increased vigor and happiness to individuals, and society in turn would be paid collective dividends through increased productivity and satisfaction levels in the populace. The payoff for effective interventions and health education among the youth is potenitally far greater than it is for an adult population: Theoretically, at least, it should be easier to establish healthful lifestyles and to prevent the formation of bad habits in the malleable young than to change existing patterns and habits in adults.

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*See Recommendation 41.

In a very real sense, Minnesota is a leader in the field of health education: The content of both a major and a minor in health education are spelled out and adhered to throughout the colleges in the state. A model curriculum has been developed at the state level which acts as a general guideline for teaching efforts in the schools. There are regulations on the number of hours of health education each student must receive from kindergarten through grade 12. A health education coordinator in each district is responsible for overseeing health education efforts. Finally, there are many health services delivered in the schools, including innoculations and experimental prevention programs in the dental area.

Without a doubt, Minnesota *is* making an effort in the health education area, but in some ways this effort remains minimal. In this age of the budget crunch, health education is nearly always a low-priority item. Few school districts have the money to spend on detailed curriculum development, so whatever education occurs is left largely up to the teacher alone. A shortage of support materials and textbooks in the field do not make the teacher's job any easier. In exploring the status of health education in schools, Commission members were told that it is not uncommon to have only a single set of textbooks available for an entire school, making it necessary for teachers to take turns using a relevant book. Furthermore, in-service training for teachers is not carried out in an organized or consistent manner because of the lack of available time and money. Teachers just coming out of colleges are better trained in health than the older teachers, but the young teachers are, of course, the first ones to go when budgets are cut. As this point, the teachers with strong backgrounds in health education are few and far between in the system. Finally, the Health Education Coordinator in each district is usually a teacher with a full-time teaching load, meaning that the time and attention he or she is able to devote to health education is understandably minimal.

Thus, despite public and official commitment to health education, the important opportunity to mold health-conscious citizens is largely being passed up in our schools. One might conjecture that health education is "too controversial" to be dealt with by groups such as school boards, which are essentially political bodies. Health education may have earned this reputation in some areas due to the fact that much of the money allocated for health education from state and federal sources focuses on sex education and drug education — two issues that divide communities into separate, warring factions. Unfortunately, making money available to only these two areas distorts the focus of comprehensive health education programs, in which subjects other than sex and drugs are equally important.

The deficiencies in health education in the schools were a matter of major concern among the Commission members, and they decided to approach the problem in a rather novel way: looking at the actual health status of our children — the outputs of the system, rather than at the things that brought it about — the rules and regulations affecting health education.

RECOMMENDATION 35: HEALTH STATUS IN SCHOOL-AGE CHILDREN

▪ Minimum standards relating to such areas as obesity, physical fitness, and chemical use should be developed for judging the health and fitness of the school-age population. Where established standards are not met, school districts should focus their curriculum development and intervention efforts in problem areas and be held accountable for meeting these standards.

The standards for health status in the school-age population should be devised by a group with extensive epidemiological experience in identifying and monitoring risk factors and lifestyle characteristics. Many approximations of the final standards and much experimentation in setting up an effective process would undoubtedly be necessary before a functioning system were to emerge. Because the "standards" referred to in this recommendation relate only to the outputs of the system, a given school district would have total flexibility to design whatever curriculum or intervention efforts were necessary to remedy its particular problems. The effectiveness of these types of programs should be readily determinable also: If a goal were to reduce the obese population from 20% to 10% of the total population, intervention efforts could be shown as either successful or unsuccessful by clearly objective measures. The approach is challenging; it will require a great deal of imagination and experiementation in the schools, but the potential rewards for a given district and for society as a whole are impressive.

Teaching Consumers to Use the Health Care Delivery System Cost-Effectively

The consumer currently has little real latitude over his or her use of most health care services since so many "decisions" to use these services are not decisions at all — they are simply the result of complying with a physician's orders. There are, however, certain things that a consumer can do to act as cost-effectively as possible:

- *Engage the services of a primary provider – that is, a physician who handles all routine medical care (family practitioners, pediatricians, obstetrician-gynecologists, and internists are generally included in this category).*
- *Seek the advice of the primary provider when it seems medically appropriate and supply the provider with adequate information.*
- *Use the health care facility appropriate to the situation.*

Each of these points will be considered separately along with its related recommendation(s).

Engage a Primary Provider. Use of a primary provider should enhance the quality of the care one receives because, presumably, this type of provider has access to a patient's medical history, is knowledgeable in selecting the best specialists for a patient's problems, can take care of many questions over the phone, and can handle simple procedures in the office where they can be done most cost-effectively. The probability of early detection of disease is also enhanced by use of a primary provider. Yet, many consumers are not under the care of a primary provider. These "floating" patients are likely to receive care of less-than-excellent quality, and they also cost the system money in the form of unnecessary testing, overly expensive procedures, and duplicate records-processing. The Commission believed that these problems could be relatively easily remedied by implementation of the following recommendation:

RECOMMENDATION 36: OBTAINING PRIMARY PROVIDERS

▪ Directories of physicians should be published by county that identify specialty, location, characteristics of practice, hospital affiliations, and sample ranges of charges. Also included in this directory should be:

- **☐ a glossary of the various specialties and subspecialties**
- **☐ a decisionmaking guide to assist the consumer in clarifying his or her needs and to familiarize him or her with questions that should be asked of any provider**
- **☐ a selection process model to guide a consumer in choosing a physician**

The purpose of these directories would be to help consumers choose wisely when "lining up" a primary physician. Once the directories are prepared, they should be well publicized and made widely available.

Seek Advice When Appropriate. If consumers would be more selective in seeking their physicians' advice, they would save themselves time and money and would simultaneously improve their chances of receiving high-quality care. At one end of the spectrum, consumers often use physicians unnecessarily to treat self-limiting illnesses or conditions that could be just as effectively handled by home treatment. This underutilizes a physician's skill and wastes both parties' time. On the other hand, consumers can also be too selective — they sometimes wait too long for treatment and see a physician when complications have arisen or the disease has reached an advanced stage that could have been avoided or prevented with earlier treatment. The key is being sensitive to the body's clues — being able to differentiate between conditions where a physician's help is and is not appropriate.

Too few people *are* sensitive to their bodies: Consumers know remarkably little about how they function, which symptoms are serious and which are not, and what illnesses a physician can effectively treat. The lack of good health education is one cause of this naiveté, but another cause is that our society has virtually stripped itself of any responsibility for health care and instead assigned it all to physicians. The Commission was of the attitude that this situation is unfortunate — that a certain amount of self-care *is* an appropriate responsibility for the consumer and that a responsible consumer should know, at the very least:

- — *when to call a physician*
- — *what to tell the physician when you call*
- — *when to go to an emergency room*

RECOMMENDATION 37: SELF-CARE FOR CONSUMERS

▪ Physicians should supply their patients with self-care handbooks and strongly encourage patients to refer to these before making an appointment or going to the emergency room.

▪ Since employers have a vested interest in seeing inappropriate utilization reduced, employers should also supply self-care handbooks and encourage employees to refer to them.

▪ Studies should be conducted to determine whether consumers who use a good self-care guide and are trained in simple data gathering and reporting techniques actually use health care services more appropriately, have higher-quality interactions with health care professionals, and experience comparable or reduced morbidity.

In order to implement the above recommendations, the self-care guides currently on the market should be reviewed by the Minnesota Medical Association, and those guides which are complete and accurate should be identified. In terms of conducting studies, direction could be taken from Blue Cross/Blue Shield, which is presently carrying out a study to determine whether self-care materials cut down on the incidence of physician visits.

Use Health Care Facilities Appropriately. The major problems in regard to use of health care facilities are excessive use of emergency rooms, prolonged stays in acute-care facilities, and use of inpatient facilities when outpatient facilities would be adequate. These problems have been addressed elsewhere in this report and have been included already in various recommendations.

In summary, the Commission believes that both the provider and the consumer have great potential to reduce or contain costs in the health care industry. The next chapter will address a final component of health care costs — government regulation.

Chaper 6

Recommendations to Improve the Cost-Effectiveness of Government Regulation

Government regulation has been mentioned several imes in this report, but mainly from the point of view of ts potential (or lack thereof) to contain costs and its unction as a barrier to competition in the marketplace. The Commission, throughout its discussions, was concerned with another aspect of government regulation — its impact on costs.

REGULATION'S GENERAL IMPACT ON COSTS

Government regulations have arisen in response to excessive cost escalation in the health care field and the need to assure minimal levels of quality in the care delivered. Both of these are legitimate concerns of government. To a considerable degree, present regula- ions represent the government's attempt to fill a vacuum eft by providers and institutions who together have either failed to police themselves sufficiently to avoid the need for regulations altogether or failed to propose ealistic regulations themselves as alternatives. Whatever the roots of regulation, there is little question that different agencies have sponsored overlapping regula- ions and in some instances, different agencies have ssued directly conflicting regulations. The net effect is a considerable amount of counterproductive effort and an *ncrease in costs* for institutions. Determining the exact cost of complying with regulations is extremely difficult because there are no precise statistical data on either the costs themselves or on the actual benefits derived from compliance.[10] As a consequence, we can only guess at he cost.

The New York Hospital Association has estimated that 25% of the costs members experience are the result of complying with various regulations. Recent studies conducted in North and South Carolina and Michigan ndicate that direct costs are approximately 1.5% to 2% of otal hospital revenues.[11] Apparently, the more heavily egulated a state is, the higher the percentage of total costs associated with regulation: Massachusetts, a heavily regulated state, experiences direct costs of 3.5% o 4%.[12] The indirect costs associated with regulation are harder to measure, but are no less striking: The ratio between federal regulatory expenditures and total compliance cost is estimated to be greater than 20 to 1 even now, and the cost of operating federal regulatory agencies is predicted to double between 1974 and 1979.[13,14]

It is apparent that with increased regulation, we may expect even higher costs. The Commission's concern, however, was not the exact percentage of cost increase that government regulation might cause, but rather that we as a society obtain maximum benefit from these regulations in terms of health, safety, and useful information. In short, we have a right to expect that the benefit gained from further government regulation is at least equal to the cost of complying with it.

RECOMMENDATION 38: GOVERNMENT REGULATION

- **Any legislation mandating health care benefits or regulation regarding health care must include the provisions below in order to be adopted by either state or federal government:**
  - ☐ **a statement of economic impact and some estimate of the benefits to be gained, and a determination of whether such benefits are priced beyond the reach of any segment of the population**
  - ☐ **public hearings at which both the legislation or regulation and the statement of economic impact can be subjected to public scrutiny and discussion of the benefits and costs**
  - ☐ **a time limit, such as five years, after which a regulation becomes null and void unless a review process, which includes public hearings, reaffirms the need for such regulation**
- **All public and private health care institutions, including state and federal, should be subject to the same regulations — such as quality assurance and utilization review requirements — as are other health care institutions.**
- **Finally, the review process above should be extended to existing legislation and regulations and a statement of the costs and benefits of each piece of legislation or regulation should be prepared by the administering agency.**

In addition to concern for the impact of regulation in general on costs, there was particular concern expressed within the Commission regarding legislation and regulation in two areas — certificate of need and allied health professionals.

Certificate of Need Legislation

Two central issues surround certificate of need legislation. First is the fact that federal and state health care institutions are not included under certificate of need legislation, and hence are free to do whatever they wish in terms of building facilities and acquiring specialized technology. Second is the question of whether certificate of need should apply to all providers, including physicians' offices and clinics. Why should a clinic be able to buy a CAT scanner, for example, when a hospital cannot? On the other hand, if certificate of need is capable of creating perverse incentives, as discussed in the first chapter of this report, it doesn't seem desirable to extend it to any more providers than are already affected.

In its discussions of these issues, the Commission agreed on two principles: first, that the law should apply equally to all providers, since this is the only way to be fair to all; and second, if the law is in fact bad, it should be so documented and changed through the combined efforts of all involved and potentially involved.

RECOMMENDATION 39: CERTIFICATE OF NEED

- **Certificate of need, if it proves to be an effective cost-control mechanism, should apply equally to all providers, including state and federal health care institutions, physicians' offices, and clinics.**

Allied Health Providers

The subject of regulation affecting allied health providers is also surrounded by two issues — reimbursement for treatment and licensure of professional status. The issues are related, because, where licensure exists, the right to be reimbursed by third party payers for professional charges usually exists as well. Thus, the issue of whether a professional group is licensed has serious economic import for that group.

In an ideal marketplace in which market forces were at work tempering consumer demand and inspiring competition on the basis of performance and price among providers, there would be no problems to deal with in regard to allied health providers other than some certification process to ensure competency and protect the health and safety of the public. In our "nonmarket," however, allied health providers are subject to the same incentives as other providers — namely, the incentive to overtreat and to charge far more than the "real" market would bear. Providers can *create demand* in this market, so the more providers, the more demand; and the more demand, the higher the costs.

It was within the context of this reality that the Commission explored the issues involved with allied health providers. No doubt, *appropriate* use of allied health providers could achieve cost-savings. However, experience has shown that allied health providers often duplicate a physician's services, resulting in increased rather than reduced charges. In addition, use of an allied health provider rather than a physician does not automatically mean that the charge for a given service will be less: Nurse practitioners in some instances are charging considerably more than physicians for certain services.

As for the issue of licensing, the practice could bring about such clearly defined roles that the provision of medical services would become overly cumbersome, as has been demonstrated in other disciplines and occupations. Rigidity of role specification has driven up costs, served to prevent the entry of newcomers into the job market, and generally failed to ensure that quality is any better than it was before. There is no reason to believe that the health care industry would respond any differently — specifically, that further demarcating professional roles by licensing allied health providers would do anything more than drive up costs in the health care field.

Furthermore, third party payers are faced with the purely practical problem of *who should be reimbursed.* If allied health providers proliferate, who would be in a position to decide who deserves reimbursement? Third party payers could conceivably be beseiged by dance therapists, transcendental meditators, exercise consultants, and "fat farms." There is no argument that many of these activities and treatments can be therapeutic, but with such a multitude of providers generating services, the decisionmaking process — of who gets what care and when — as well as the responsibility for rendering care could become unduly diffuse. It could become virtually impossible for the third party payers to determine whether care rendered warranted reimbursement under their contract. Thus, from the third party payer's point of view allied health providers should be reimbursed only when they are under the direct supervision of a physician.

This brings up the question of what direct supervision is. Essentially it means that a physician delegates the responsibility for rendering a particular treatment to an allied health provider but retains full legal and professional responsibility for the services provided. The physician thus has the responsibility to audit the quality, the safety, and the cost-effectiveness of care. It would be in the physician's own interest then, to delegate services wisely.

Because of the tremendous complexities inherent in the area of licensing and reimbursing allied health providers, the Commission was hesitant to do more than endorse principles in the following recommendation:

RECOMMENDATION 40: ALLIED HEALTH PROVIDERS

▪ Ideally, allied health providers should not be used unless it is demonstrated that their involvement is cost-effective or remedies a maldistribution in services.

▪ Allied health providers should not be reimbursed directly unless they are under the supervision or authorization of a physician.

▪ Licensing of allied health providers should occur only when it is absolutely clear that public safety depends on it. Even then the issue of licensing should be recognized as mainly an economic one.

▪ No legislation should be passed that inhibits a physician's use of allied health providers.

▪ Physicians should consider new ways to use allied health providers to deliver high quality care in more efficient ways.

▪ Careful study should be made of the supply of and demand for allied health providers, and state funding should not be made available to training programs unless the demand for the graduates is clearly demonstrated.

In general, the Commission thought that the state legislature needed to be extremely careful in mandating benefits that specify reimbursement of particular allied health providers. In line with the thrust of their views on regulation in general, the Commission felt that careful consideration of the costs involved would be appropriate before more benefits designating reimbursement for specific services were mandated.

Chapter 7

Implementing the Commission's Recommendations

The Commission on Health Care Costs has expressed a desire to turn over its recommendations at the end of 978 to an ongoing body charged with their implementaion. This follow up to the recommendations might nclude legislative activity, interaction between state gencies and the private sector, negotiation with nsurance carriers, and a number of other initiatives.

Numerous suggestions have been made as to the kind of body that should be formed to carry out this task as well s the sponsor of such a mechanism. The following ecommendation is represenative of the feeling of some Commission members that the Minnesota Medical Association should continue to shoulder the primary esponsibility for addressing the health care cost problem n the state. However, the following recommendation, if mplemented, would produce an entity entirely separate rom the Minnesota Medical Association and whose ctivities were completely independent of their control.

RECOMMENDATION 41: HEALTH CARE COALITION

- **A nonprofit, tax-exempt Coalition should be established to implement the recommendations of the Commission on Health Care Costs and to monitor health care cost trends in Minnesota so that additional actions may be taken where appropriate.**
  - ☐ **The Coalition should be created by the Commission through a special implementing body of three members including the current Commission Chairman. This implementing committee of the Commission on Health Care Costs should be responsible for naming individuals to serve on the Coalition Board of Directors, establishing the number of directors to be appointed, developing guidelines for Coalition activity, approving the first budget in conjunction with the Coalition Board, and arranging for outside financing for the first year. The implementing committee should complete its work following the first meeting of the Coalition Board of Directors.**
  - ☐ **The budget for the first year should be raised primarily from sources outside the medical profession, and the initial staff should consist of — at least — an Executive Director and one secretary.**
  - ☐ **The Coalition should prepare an annual report to be submitted to the full Commission on Health Care Costs. The latter group should be reconvened in a year to hear this report.**

Through the work of such a Coalition, the diverse interests of all groups affected by the other recommendations could be brought together and treated equitably. Its efforts might serve as a model to the nation of a workable means of implementing the complex actions necessary to bring health care costs under control.

In Conclusion, the Commission on Health Care Costs offers the foregoing recommendations to the Minnesota health care community with the hope that significant effort will be afforded their adoption and implementation, and with the hope that they will provide the basis for controlled costs and improved performance of the health care system in the state and in the nation.

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APPENDIX A: BIOGRAPHICAL NOTES ON MEMBERS OF THE COMMISSION

Richard J. Frey, M.D., served as Chairman of the Commission on Health Care Costs and is also the Chairman of the Minnesota Medical Association's Board of Trustees and a member of the Board of Directors of the Metropolitan Medical Center in Minneapolis. An internist, Dr. Frey has been the President of the Hennepin County Medical Society, the Minneapolis Society of Internal Medicine, the Minneapolis Academy of Medicine, and the Minnesota Association of Internists.

Chester A. Anderson, M.D., is the Immediate Past President of the Minnesota Medical Association. He has been Chairman of the Association's Committee on Legislation and has held several other important posts within the Association's committee structure. Dr. Anderson is a family practitioner in Hector, Minnesota, and is a member of that community's Chamber of Commerce.

Richard E. Anonsen, M.D., a Past President of the Minnesota Medical Association, is in family practice in Minneapolis. He was the founder, President, and Chairman of the Board of the Foundation for Health Care Evaluation, and has been President and Chairman of the Board of the Hennepin County Medical Society, Chief of Staff and member of the Board of Trustees at Eitel Hospital, and an alternate delegate to the AMA.

James E. Bormann recently retired from his post as Director of News and Public Affairs at WCCO radio. He has served on the Board of Directors for the Hennepin County Red Cross for the past 13 years, and has been on the boards of the Citizens Council on Crime and Delinquency, the State Health Department, the Viking Council of the Boy Scouts of America, the Minnesota Heart Association, and the Citizens League of Minneapolis. Other activities have included membership on the Supreme Court Advisory Committee on Continuing Legal Education for State Court Personnel and on the Board of the Minneapolis Citizens Committee on Public Education.

Daniel V. Dodge is Superintendent of Personnel Services for the Minnesota Ore Operations of the United States Steel Corporation in Mountain Iron, Minnesota, where he has been responsible for the administration of the company's insurance and medical programs for 20 years. He is also a member of the Northeastern Vocational Organization.

Photo not available

Earl G. Dresser is President of Methodis Hospital in St. Louis Park, Minnesota. As hospital administrator, Mr. Dresser has serve on numerous committees of the Minnesot Hospital Association and as a member of th Blue Cross/Blue Shield Value Assurance Committee. In addition, he is a member of the West Suburban Chamber of Commerce.

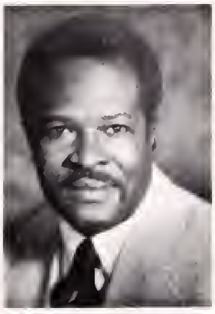
Robert S. Flom, M.D., a St. Paul surgeon, i President of the Minnesota Medical Association. Dr. Flom is a Past President of the Ramsey County Medical Society and active in many programs of the Minnesota Medical Association. He is a delegate to the House of Delegates of the American Medical Association and a member of the Board at St. John's Hospital in St. Paul.

Robert Hanson currently serves as control operator for Reserve Mining Company in Silver Bay, Minnesota, and is a member of the Board of Directors of the Group Health Association of Northeastern Minnesota. He was County Commissioner for Lake County from 1964 to 1972, on the Statewide Board of Directors of County Commissioners for four years, Director of the Board of Minnesota Lutheran Social Services for 3 years, and President of the U.S. Steel Workers Local #5296 during the first 8½ years following its formation.

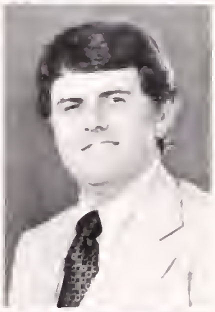
James L. Hetland, Jr., is Senior Vice President of the First National Bank of Minneapolis. He is a Board member of Interstudy, the National Association of Employers on Health Maintenance Organizations, and Public Service Options. Mr. Hetland was the first chairman of the Metropolitan Council and is currently a member of the Rotary Club, the Citizens League, the Downtown Council of Minneapolis, and the Freshwater Biological Research Foundation.

Donald Kissack, Group Insurance Manager for the 3M Company in St. Paul, is on the Board of Directors of the Minnesota Comprehensive Health Association and a Director of the National Association of Employers on Health Maintenance Organizations. Mr. Kissack is also a member of the Council on Employee Benefits Section and the Washington Business Group on Health.

obey Lapakko serves as Coordinator of onsumer Affairs for the Minnesota AFL-CIO. he served as the Director of the Consumer ervices Section of the Minnesota Department f Commerce under Governor Rudy Perpich, nd before this served on the Governor's dvisory Council on Consumer Affairs. Long ctive in consumer affairs, Mrs. Lapakko has cted as an advocate on a wide range of issues or the Minnesoa AFL-CIO and became Direc- or of its new Consumer Affairs Department in uly, 1977. She helped organize both the onsumer Federation of America' and the innesota Consumers League, of which she vas president for 6 years.



enator B. Robert Lewis, a Doctor of Veterinary ledicine, is a State Senator from the 41st istrict. He has been active in civic affairs, erving on the Chamber of Commerce, the St. ouis Park Planning Commission, the Urban eague, the State Board of Education, and the t. Louis Park Human Relations Council. In his resent position, he has been Vice Chairman of ne Finance Committee and Chairman of the inance Committee of Health, Welfare, and orrections.



hillip A. Little is Senior Vice President of dministration of Blue Cross/Blue Shield of innesota. He serves on the Metro Community lealth Consortium Board, and was a member f the Minnesota Hospital Association's Study n Hospital Expectations. Mr. Little was also ecently on the United Hospitals' Ad Hoc omputer Advisory Committee.

alter McClure, Ph.D., is a Senior Policy nalyst and Director of the Health Policy and lanning group of Interstudy in Excelsior, innesota. His primary specialties are research nd policy on health care delivery and financ- g, with emphasis in the areas of organized stems of care, the evaluation of medical care y outcomes, and national health insurance. He as been a consultant to HEW and to various ongressional committees on developing MO and other health legislation. He has also ted as a consultant to a number of developing MOs, has addressed dozens of audiences on ealth policy issues, and has authored numer- us papers in this field. Dr. McClure is a ember of the Citizens League and Public ervice Options.

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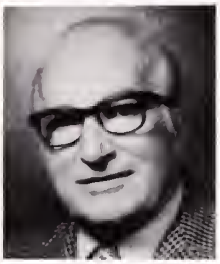
avid F. McIntire is Corporate Manager of nployee Benefits for General Mills in Min- apolis. He is Past President of the National ssociation of Employers on Health Mainte- ance Organizations, Chairman of the Sub- mmittee on Health Delivery Systems of the hamber of Commerce of the United States, a ember of a Special Commmittee on the ation's Health Care Needs of the U.S. hamber, and a member of the Washington siness Group on Health. Mr. McIntire has ne special work on the impact of HMO tions for General Mills and employees.

Glen D. Nelson, M.D., is President and Chairman of the Board of Trustees of the St. Louis Park Medical Center. A surgeon, Dr. Nelson is a member of numerous professional organizations and is a member of the Executive Committee of Interstudy. He also serves on the boards of Methodist Hospital Foundation, MedCenter Health Plan, St. Louis Park Medical Center Research Foundation, and the Walker Art Center. In addition, he is a member of the Board of Regents of St. John's University and a clinical instructor at the University of Minnesota Medical School.

John E. Pearson is President and Chief Executive Officer of the Northwestern National Life Insurance Company headquartered in Minneapolis. He has served as Chairman of the Council on Consumer and Professional Relations of the Health Insurance Association of America and as a member of the Public Relations Policy Committee of the Health Insurance Institute. He is Chairman of the Minneapolis Urban Coalition and a Board member of St. Mary's Extended Care Center, the Minneapolis Chamber of Commerce, the Minneapolis Metropolitan Housing Corporation, and Methodist Hospital.

Donald L. Shovein is Director of Corporate Employee Benefits of the Control Data Corporation of Minneapolis. He is a member of the Board of Directors of the Foundation for Health Care Evaluation and a member of the Rate Review Panel of the Minnesota Hospital Association.

Jean H. Smelker, M.D., is Center Director for the Community-University Health Care Center of the University of Minnesota. Dr. Smelker is a member of the Metropolitan Health Board and the American Lung Association and currently enrolled in the Masters of Public Health Program in Medical Care Organization at the University of Michigan in Ann Arbor. Her studies in this area focus on health issues and health policies.



Martin Van Herik, M.D., is a consultant in therapeutic radiology at the Mayo Clinic in Rochester, Minnesota. He is Past Chairman of the Committee on Medical Service of the Minnesota State Medical Association and serves on the Medical Insurance Committee of the Mayo Clinic and the Committee on Medical Economics and Insurance of the Minnesota Radiological Society.

Ronald C. Young, M.D., is Medical Director of the Minnesota Department of Public Welfare and an Associate Professor in the University of Minnesota Medical School. Dr. Young is a board member of the Foundation for Health Care Evaluation in Minneapolis and is a former member of the Metropolitan Council's Health Board. He is also a former member of the St. Paul Mayor's Committee on Health Planning.

PPENDIX B: TEXT OF THE RECOMMENDATIONS

ECOMMENDATION 1: Organize New Health Care lans

Employers, insurers, providers, and interested community aders should support the development of new and existing ealth care plans by providing managerial and marketing expertise — and financial support, if necessary — to providers who are forming new plans.

- Providers should review both the existing health care plans and proposed health care plans to identify those plans that may be consistent with their own style of practice. The Commission urges physicians to seriously consider participating in such plans.

RECOMMENDATION 2: Promote Market Forces

- Employers offering health benefits should create a fair market for health care plans by offering their employees multiple choices among conventional insurance plans and alternative health care plans. In order to insure that fair market conditions prevail among these choices, the following conditions must be met:
  - ☐ the employer should contribute the same amount of money toward the premium of every choice available
  - ☐ the difference between that amount and the chosen plan's actual premium should be paid by the employee or returned to him or her in another benefit form depending on whether the premium is more or less than the employer's contribution
- Unions should negotiate for multiple choice in their contracts to insure that each employee has individual choice of the plan best suited to his or her needs.
- Employers and unions should actively promote the concept of choice to employees and provide simple, comparative information about all available choices.
- The market and the opportunity to make fair market choices should be expanded quickly to all consumers including, but not restricted to, the groups below:
  - ☐ Medicare/Medicaid recipients
  - ☐ employees whose employers offer low benefit packages or do not offer health care benefits
  - ☐ the self-employed
  - ☐ part-time employees
  - ☐ government employees

RECOMMENDATION 3: Eliminate Barriers to a Competitive Marketplace

- Competitive bidding among hospitals should be encouraged, provided that:
  - ☐ the competition is subject to the same rules as are other competitive industries and as permitted under the laws of Minnesota
  - ☐ private paying patients are not subsidizing groups
- Health care plans should have the latitude to design whatever set of benefits and premium charges they deem most marketable in a given employee population.
- Legislation and regulation that limit the flexibility of the individual delivery system should be discouraged, and existing laws and regulations that have this effect should be repealed or amended. Recognizing legitimate differences between health care plans and insurance plans, the Commission believes that laws should have an equivalent effect on the marketing of each.

RECOMMENDATION 4: Institute Cost-Sharing**

- All insurance plans or health care plans offered within the state should have cost-sharing provisions specifically directed toward discouraging immoderate or indiscriminate use of services. Cost-sharing should not, however, be a barrier to necessary therapeutic and preventive care. In addition, any secondary coverage eliminating appropriate cost-sharing should be discouraged within the state. Lastly, employees should be offered a choice of plans that utilize different amounts of cost-sharing and those differences should be reflected in the plans' respective premiums.

RECOMMENDATION 5: Utilization Review

- Major employers in the state should exert pressure on major insurers to take steps to reduce inappropriate utilization.

RECOMMENDATION 6: Second Surgical Opinions

- The Minnesota Medical Association should evaluate th studies done on second surgical opinion programs and monit the results of the pilot testing presently being conducted withi the state and elsewhere. Should the data indicate that eith substantial cost-savings or improvement in the quality of car are possible, the Medical Association should make stron recommendations to employers and insurers that this progra be adopted — possibly on a mandatory basis — throughout th state. Should the program be determined to be without mer either in terms of cost or quality, then the program should b disbanded.

RECOMMENDATION 7: Feedback for Physicians

- The Foundation for Health Care Evaluation should include i the patterns of practice that are presently being generate criteria for cost-effectiveness as well as for quality. In addition each practicing physician should be supplied with distributor of aggregate data and his or her own personal profile t compare with these distributions.

RECOMMENDATION 8: Hospital-Based Physician Compensation

- Hospitals and their medical staffs should re-examine thei compensation arrangements with contracted hospital-base physicians and devise compensation systems that encourag cost-sensitivity. Placing these contracted physicians on a fixe salary may be the first step in this direction.

RECOMMENDATION 9: Health Promotion by Physicians

- Analysis of risk factors and lifestyle characteristics should b included in the routine physical examinations given by ever primary provider in the State of Minnesota. This analysi should include such determinations as:
  - ☐ smoking habits
  - ☐ physical activity level
  - ☐ nutritional pattern
  - ☐ chemical usage (alcohol, caffeine, drugs, etc.)
  - ☐ weight, blood pressure, cholesterol levels, etc.
- Should a patient be determined to have risk factors, th physician should advise the patient to work on reduction of th risk factors and refer him or her to behavioral counselors withi the physician's clinic or outside agencies specializing in suc interventions.

RECOMMENDATION 10: Health Promotion by Industry

- Major industry should actively experiment with healt promotion programs in order to counteract the problems o absenteeism, excess numbers of sick days, and rising healt insurance premiums. Some methods that should be considere are:
  - ☐ development of in-house health promotion programs
  - ☐ selection of reputable programs in the community an sharing of the fees for such programs with employees providing that their attendance is good and that objectiv changes in risk factors last over sufficiently long periods t demonstrate that the changes are not temporary
  - ☐ careful evaluation of the impact of these programs o morbidity, disability, absenteeism, productivity, etc.
  - ☐ encouraging employees by means of incentives (fo example, bonuses, earned days off) to participate i programs or "healthful" behavior patterns that demonstrat cost-effectiveness

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**See Appendix C for dissenting comment.

ECOMMENDATION 11: Health Promotion by Third arty Payers

Health insurance carriers should conduct pilot studies on ing premium charges to risk factors and lifestyle characteris-cs such as smoking patterns and level of physical activity. articular attention should be paid to those risk factors under e control of the individual. Furthermore, third party payers hould review intervention programs and identify their ost-effectiveness. Should the programs be determined to be ost-effective, third party payers should consider extending overage to them.

ECOMMENDATION 12: Length of Stay

Hospitals should perform concurrent utilization review and uality assurance review (retrospective quality audits) for a ample of patients regardless of payment source.

During concurrent review, should the care already rendered e found to be obviously inappropriate, the hospital and the ttending physician should be at risk. If the provider indicates o the patient that additional hospital care is not medically ndicated, the patient should be advised that any additional are will have to be paid for at his or her expense. Should etrospective review reveal a repeated pattern of overutiliza-ion, a program of sanctions should be implemented in the nstitution involved.

ECOMMENDATION 13: Treatment Modalities

- The medical specialty societies in Minnesota should define cceptable treatment modalities and conduct controlled studies vith clearly defined protocols to determine the costs and enefits of these various modalities, including the alternative of o treatment whatsoever. Such factors as quality of life and nprovement in productivity should be measured along with norbidity and cost in the studies.

- Reimbursement for existing treatment modalities should ontinue only if the professionals involved are willing to articipate in such studies. Furthermore, all new treatment nodalities should go through such an evaluation process prior o reimbursement by third party payers, and no new clinical reatment should be approved for reimbursement without its ost-effectiveness demonstrated. In cases of dispute regarding eimbursement, the third party payers could turn to the pecialty societies for judgment.

ECOMMENDATION 14: Clinical Practices

- Agencies and federal, state, and private foundations which und studies of clinical practices should require cost-benefit nalyses and rigorous outcome evaluations in grant work.

ECOMMENDATION 15: Graduated Levels of Care

- Third party payers should promote development of adequate nsurance coverage for high quality care rendered in the most ost-effective setting. Among the types of services to which overage should be extended — provided that they are lemonstrated to produce a net reduction in services rendered, hus reducing the cost of health care to the community as a vhole — are:
  - ☐ health services delivered out of a hospital setting
  - ☐ skilled intermediate services and facilities
  - ☐ home health care
  - ☐ ambulatory care
  - ☐ hospices
  - ☐ community services provided by hospitals

ECOMMENDATION 16: Preadmission Testing

- Third party payers should encourage preadmission testing on an outpatient basis in order to reduce hospital utilization. These tests should be of high quality and performed in the most appropriate setting. Reimbursement should be made on the most favorable basis under the contract, which may mean modifying or waiving both the deductible and the coinsurance clause.

RECOMMENDATION 17: Emergency Room Utilization

- Physicians should explore ways to reduce emergency room usage by their patients by considering such policies as:
  - ☐ "lunch hour" coverage in physicians' offices to avoid unreferred emergency room visits
  - ☐ shared telephone screening systems with other physicians within a practice or with other practices in the area
  - ☐ lengthened office hours on a rotating basis in either physicians' offices or clinics and, if necessary, appropriate arrangements with other offices that are geographically proximate, to lengthen the "business day"
- Third party payers should penalize indiscriminate use of the emergency room by:
  - ☐ adding appropriate copayments or deductibles to emergency room use
  - ☐ eliminating favorable treatment (reimbursement) of procedures done in the emergency room instead of in a physician's office
- Physicians in the emergency room should:
  - ☐ conduct no investigative work without first contacting the patient's physician, except in cases of real emergency
  - ☐ advise the patient to get a primary care physician if he or she does not have one
- Consumers should be furnished with a self-diagnostic handbook that advises them when to call a physician and what to tell him or her, and when to go to the emergency room.
- Last, a public campaign should be undertaken to inform consumers of the excessive costs of emergency room use and of the benefits both in cost and in quality of care attainable through having a primary provider.

RECOMMENDATION 18: Emergency Room Practices

- Every hospital having an emergency room should review both its staffing patterns and its modes of practice, and institute whatever changes may be indicated to increase cost-effectiveness.

RECOMMENDATION 19: Hospital Capacity Reductions

- Recommended reductions in hospital capacity in a community should be based on a generally accepted policy framework; careful measurement of community needs; a cost-effective priority system; a plan for resolving such issues as resulting unemployment, debt payment, and retention of health care professionals within the community; and, finally, a proposal that has been agreed upon by key parties in the community health care system for an orderly process of carrying out the overall strategy.

RECOMMENDATION 20: Reducing Capacity in Rural Areas

- A study focusing on the hospitals outside the seven county metropolitan area should be undertaken by the State Health Planning and Development Agency. This study should evaluate the social, economic, professional, and legal implications of:
  - ☐ closing entire hospitals
  - ☐ sharing services between hospitals
  - ☐ closing services within a single hospital

RECOMMENDATION 21: Financial Compensation for Closure

- If publicly mandated closure forces a hospital to close on the basis of excess capacity alone and it is demonstrated that the bondholders or other creditors will suffer economic loss despite sale of land or building, then public funds should be made available from the state and/or federal government to provide relief.

RECOMMENDATION 22: Revising Hospital Rate Structures

- The hospital rate structure for acute-care services should be modified so that revenue produced by specific services covers the cost of providing those services, thereby preventing — insofar as possible — the subsidizing of services not producing enough revenue to meet their costs.

RECOMMENDATION 23: Medicare/Medicaid Reimbursement

- Medicare and Medicaid should reimburse institutions on a basis that discourages subsidy by private-paying patients.

RECOMMENDATION 24: An Information Clearinghouse

- An information clearinghouse should be established that identifies and locates literature on the latest strategies and techniques in the area of hospital administration, and literature reviews on selected subjects should be available upon request.
- Hospitals should use these services and adopt promising techniques as they are identified.

RECOMMENDATION 25: Hospital Boards

- Members of the Board of Directors of hospitals should become even more active in promoting strategies for cost containment in the hospitals. They should make increasing demands on administrators for well-thought-out plans for cost analyses, efficient staff allocations, and means of reducing capacity such as merging, consolidations, and sharing services with other hospitals.

RECOMMENDATION 26: Desirable Practice Patterns

- Criteria for desirable patterns of cost-effective practice should be developed for broad disease categories. Once developed, the criteria should be published in the professional journals to increase their dissemination and utilization.

RECOMMENDATION 27: Medical School Curricula

- Once the criteria for desirable practice patterns for various disease categories are developed, they should be incorporated in the proper courses in medical school curricula. Criteria should be developed first for inclusion in the basic clinical courses required of most medical students.

RECOMMENDATION 28: Clinical Reviews and Case Presentations

- As the criteria for cost-effective patterns of practice are developed, they should be incorporated in clinical reviews. Evaluation of case presentations should include consideration of these criteria as well, and they should take their place alongside clinical indications in discussions of adequacy of care rendered.

RECOMMENDATION 29: Board Examinations

- Where testing for cost-sensitivity is not already included in the clinical management portion of board examinations, the specialty boards of the Licensing Committee of Graduate Medical Education who accredit residency programs should develop such testing mechanisms. Furthermore, inefficient and redundant choices of procedures should be heavily penalized in the scoring of such exams.

RECOMMENDATION 30: Continuing Medical Education

- As the criteria for cost-effective patterns of practice are established, they should become an integral and substantial part of Continuing Medical Education programs. In specific Continuing Medical Education courses, physicians should be required to consider the costs implicit in the procedures under discussion.

RECOMMENDATION 31: Cost-Effectiveness in Audits

- As the criteria for cost-effective patterns of practice are developed, they should be included routinely in audits of medical quality.

RECOMMENDATION 32: Laboratory and Radiology Use

- A guide should be developed to aid physicians in making cost-effective choices regarding laboratory procedures in the context of an entire episode of care. This guide should contain information about the specificity, sensitivity, approximate price, and any other useful information that might aid the physician in deciding whether to use a procedure or which of two or more procedures to use.
- A similar guide containing analogous information should be developed for radiology procedures.

RECOMMENDATION 33: Cost-Sensitizing

- Hospital administrators and their medical personnel should devise plans to sensitize their staffs to the costs of procedures typically performed in each department. This "sensitizing" process should occur frequently enough so that physicians and other staff are kept current on costs.

RECOMMENDATION 34: Health Promotion Task Force

- The Health Care Coalition (see Recommendation 41) should establish a *temporary* Health Promotion Task Force charged with two main responsibilities:
  - to identify how a health promotion strategy may best be developed and implemented through the state
  - to evaluate the cost-effectiveness of intervention programs that already exist and design an evaluation system to uniformly monitor the cost-effectiveness of new intervention programs across the state

RECOMMENDATION 35: Health Status in School-Age Children

- Minimum standards relating to such areas as obesity, physical fitness, and chemical use should be developed for judging the health and fitness of the school-age population. Where established standards are not met, school districts should focus their curriculum development and intervention efforts in problem areas and be held accountable for meeting these standards.

RECOMMENDATION 36: Obtaining Primary Providers

- Directories of physicians should be published by county that identify specialty, location, characteristics of practice, hospital affiliations, and sample ranges of charges. Also included in this directory should be:
  - a glossary of the various specialties and subspecialties
  - a decisionmaking guide to assist the consumer in clarifying his or her needs and to familiarize him or her with questions that should be asked of any provider
  - a selection process model to guide a consumer in choosing a physician

ECOMMENDATION 37: Self-Care for Consumers

Physicians should supply their patients with self-care andbooks and strongly encourage patients to refer to these efore making an appointment or going to the emergency oom.

Since employers have a vested interest in seeing inappropri-te utilization reduced, employers should also supply self-care andbooks and encourage employees to refer to them.

Studies should be conducted to determine whether consum-rs who use a good self-care guide and are trained in simple ata gathering and reporting techniques actually use health are services more appropriately, have higher-quality interac-ons with health care professionals, and experience compara-le or reduced morbidity.

ECOMMENDATION 38: Government Regulation

Any legislation mandating health care benefits or regulation egarding health care must include the provisions below in rder to be adopted by either state or federal government:

- ☐ a statement of economic impact and some estimate of the benefits to be gained, and a determination of whether such benefits are priced beyond the reach of any segment of the population
- ☐ public hearings at which both the legislation or regulation and the statement of economic impact can be subjected to public scrutiny and discussion of the benefits and costs
- ☐ a time limit, such as five years, after which a regulation becomes null and void unless a review process, which includes public hearings, reaffirms the need for such regulation

All public and private health care institutions, including state nd federal, should be subject to the same regulations — such s quality assurance and utilization review requirements — as re other health care institutions.

Finally, the review process above should be extended to xisting legislation and regulations and a statement of the costs nd benefits of each piece of legislation or regulation should be repared by the administering agency.

ECOMMENDATION 39: Certificate of Need

Certificate of need, if it proves to be an effective cost-control echanism, should apply equally to all providers, including ate and federal health care institutions, physicians' offices, nd clinics.

ECOMMENDATION 40: Allied Health Providers

Ideally, allied health providers should not be used unless it is emonstrated that their involvement is cost-effective or emedies a maldistribution in services.

Allied health providers should not be reimbursed directly nless they are under the supervision or authorization of a hysician.

Licensing of allied health providers should occur only when is absolutely clear that public safety depends on it. Even then e issue of licensing should be recognized as mainly an conomic one.

No legislation should be passed that inhibits a physician's se of allied health providers.

Physicians should consider new ways to use allied health roviders to deliver high quality care in more efficient ways.

Careful study should be made of the supply of and demand r allied health providers, and state funding should not be ade available to training programs unless the demand for the raduates is clearly demonstrated.

RECOMMENDATION 41: Health Care Coalition

- ■ A nonprofit, tax-exempt coalition should be established to implement the recommendations of the Commission on Health Care Costs and to monitor health care cost trends in Minnesota so that additional actions may be taken where appropriate.
- ■ The Coalition should be created by the Commission through a special implementing body of three members including the current Commission Chairman. This implementing committee of the Commission on Health Care Costs should be responsible for naming individuals to serve on the Coalition Board of Directors, establishing the number of directors to be appointed, developing guidelines for Coalition activity, approving the first budget in conjunction with the Coalition Board, and arranging for outside financing for the first year. The implementing committee should complete its work following the first meeting of the Coalition Board of Directors.
- ■ The budget for the first year should be raised primarily from sources outside the medical profession, and the initial staff should consist of — at least — an Executive Director and one secretary.
- ■ The Coalition should prepare an annual report to be submitted to the full Commission on Health Care Costs. The latter group should be reconvened in a year to hear this report.

APPENDIX C: DISSENTING COMMENTS

The following minority statement was received from Mrs. Tobey Lapakko, Coordinator of Consumer Affairs, Minnesota AFL-CIO, in regard to Recommendation 4: Cost-Sharing.

> "Although the Commission held many meetings and heard from many individuals who provided testimony and input to the Commission, there was, at no time, any documentation or specific data presented which speaks to the allegation contained in [Recommendation 4] that there is misuse by the consumers of their health insurance plans, nor that it has a significant impact on the cost of services. Traditionally, fringe benefits, which include the health care plans, have been negotiated between labor and management and are considered part of the overall wage package. Employees understand that there is a trade-off between the amount of money that is invested in a given fringe package.
>
> I am also concerned that the recommendation will result in an undue financial hardship against citizens in the State of Minnesota who are least able to assume any further financial obligations. Today's medical costs make health insurance a required purchase. Although the Commission felt that they had addressed this concern when they included the sentence 'that cost sharing should not be a barrier to necessary therapeutic and preventive care,' it does not address itself to the fact that low-income individuals wish to retain their dignity and their privacy and not be subjected to contacting welfare and/or other social agencies in order to implement this portion of the recommendation.
>
> Additionally, it should be cited for the record that the organized labor movement at both the state and national level, have been and are on record for the payment of health care benefits from dollar one."

APPENDIX D: SELECTED READINGS ON ISSUES DISCUSSED IN THIS REPORT

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